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A risk-predictive model for obstructive sleep apnea in patients with chronic obstructive pulmonary disease

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Background: Obstructive sleep apnea syndrome (OSA) is increasingly reported in patients with chronic obstructive pulmonary disease (COPD). Our research aimed to analyze the clinical characteristics of patients with overlap syndrome (OS) and develop a nomogram for predicting OSA in patients with COPD.

Methods: We retroactively collected data on 330 patients with COPD treated at Wuhan Union Hospital (Wuhan, China) from March 2017 to March 2022. Multivariate logistic regression was used to select predictors applied to develop a simple nomogram. The area under the receiver operating characteristic curve (AUC), calibration curves, and decision curve analysis (DCA) were used to assess the value of the model.

Results: A total of 330 consecutive patients with COPD were enrolled in this study, with 96 patients (29.1%) confirmed with OSA. Patients were randomly divided into the training group (70%, $n = 230$) and the validation group (30%, $n = 100$). Age [odds ratio (OR): 1.062, 1.003–1.124], type 2 diabetes (OR: 3.166, 1.263–7.939), neck circumference (NC) (OR: 1.370, 1.098–1.709), modified Medical Research Council (mMRC) dyspnea scale (OR: 0.503, 0.325–0.777), Sleep Apnea Clinical Score (SACS) (OR: 1.083, 1.004–1.168), and C-reactive protein (CRP) (OR: 0.977, 0.962–0.993) were identified as valuable predictors used for developing a nomogram. The prediction model performed good discrimination [AUC: 0.928, 95% confidence interval (CI): 0.873–0.984] and calibration in the validation group. The DCA showed excellent clinical practicability.

Conclusion: We established a concise and practical nomogram that will benefit the advanced diagnosis of OSA in patients with COPD.

KEYWORDS

sleep apnea syndrome, chronic obstructive pulmonary disease, overlap syndrome, nomogram, risk factors

Introduction

Chronic obstructive pulmonary disease (COPD) combined with obstructive sleep apnea (OSA) is called overlap syndrome (OS), which was first proposed by Flenley in 1985 (Buist et al., 2007). OS is a disease with a high prevalence ranging from 2.9% to 65.9% (Shawon et al., 2017), with reduced diagnoses, mainly due to the lack of attention of patients and doctors and the limitation of screening tools, especially in underdeveloped areas. There are considerable differences in epidemiology, treatment, and prognosis between patients with COPD alone and patients with OS. Compared with patients with COPD alone, patients with OS have been reported to have a higher risk of cardiovascular disease, increased rate of COPD exacerbation, hospitalization, mortality, and medical costs (Hong et al., 2020; Tang et al., 2021; Zhang et al., 2022). Fortunately, studies suggest that treatment with positive airway pressure therapy significantly reduced these risks and improved patients' prognosis (Marin et al., 2010; Suri and Suri, 2021; Sterling et al., 2022). Therefore, early diagnosis and the use of non-invasive positive pressure ventilation (NPPV) are beneficial to the treatment and prognosis of patients with OS.

The gold standard in the diagnosis of OSA is polysomnography (PSG), but the lack of a large-scale laboratory in developing areas and the related costs have led to a delay in the diagnosis. The well-designed questionnaires such as Sleep Apnea Clinical Score (SACS) and modified Epworth Sleepiness Scale (mESS) have been applied as an alternative method to diagnose OSA in the absence of PSG, but they were subjective and prone to bias as revealed by a meta-analysis (Chiu et al., 2017).

Therefore, there is an imperative need for a simple and reliable method to identify and triage patients with OS to guide further treatment. To this end, we analyzed the clinical characteristics of patients with OS and also developed and validated a nomogram, aiming to provide a practical tool for rapid recognition of OSA in patients with COPD.

Methods

Study population

The patients confirmed with COPD presented in our emergency department from March 2017 to March 2022 due to a recent deterioration of cough, expectoration of phlegm, and shortness of breath were consecutively enrolled in this study. Exclusion criteria included those as follows: 1. Patients with other severe diseases which might also cause dyspnea, such as congestive heart failure, interstitial lung diseases, myasthenia gravis, and severe kidney or liver disease; 2. Patients with a history of NPPV dependency; 3. Patients with incomplete clinical data; 4. Pregnancy; and 5. Patients who refuse to receive overnight sleep tests. A total of 330 participants were included, all of whom completed questionnaires and post-recovery overnight sleep cardiorespiratory monitoring. The subjects' medical history, laboratory chemistries, and other relevant information were recorded.

This study was approved by the Medical Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (2016S0130) and was conducted in accordance

with the ethical standards outlined in the 1964 Declaration of Helsinki and subsequent amendments. All subjects signed a written informed consent form before participating in the study.

Data collection

Demographic data including name, age, gender, body mass index (BMI), neck circumference (NC), and medical history were collected. Furthermore, blood samples and spirometry results were collected. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage defined by the guideline was used to measure the severity of COPD (Singh et al., 2019).

Questionnaires

All questionnaires used the validated version in Chinese. The modified Medical Research Council (mMRC) dyspnea scale was used to evaluate the degree of dyspnea, and an mMRC score of ≥ 2 was considered as the critical value of severity (Vogelmeier et al., 2017). The COPD assessment test (CAT) was used to assess the degree of health impairment. A CAT score of ≥ 10 prompts that medical intervention is needed (Kwon et al., 2013). The Sleep Apnea Clinical Score was used to evaluate the probability of OSA (Flemons et al., 1994), and a score of ≥ 5 suggests that sleep monitoring is recommended (Gali et al., 2009). The modified Epworth Sleepiness Scale was used to assess excessive daytime sleepiness (Johns, 1993; Zhang et al., 2011), and an mESS score of ≥ 10 is considered to be indicative of daytime sleepiness. Using the Pittsburgh Sleep Quality Index (PSQI) to estimate the quality of nighttime sleep (Buysse et al., 1989), with five points as the threshold, the lower the score is, the better the sleep quality is.

Sleep study

A sleep study was not done until the patient's condition became stable when no more oxygen administration or NPPV was needed. The overnight cardiorespiratory monitoring was done by a portable monitoring (PM) device (type 3, Alice PDx, Respiromics Inc. Murrysville, USA), and its accuracy has been experimentally confirmed (Nigro et al., 2013). The device includes a thermistor to monitor oronasal airflow and snoring, two bands for respiratory inductive plethysmograph determined by the ribcage and abdominal movements, a pulse oximeter, and an accelerometer to record body position. All sleep study records were manually scored by three experienced researchers (WW, SY, and PT) and validated by a senior expert (JZ) and conformed to the American Academy of Sleep Medicine (AASM) 2012 standards (Berry et al., 2012) and AASM position statement 2018 (Malhotra et al., 2018). The diagnosis of OSA can be established if the apnea-hypopnea index (AHI) is ≥ 5 /h alone with typical clinical symptoms.

TABLE 1 Demographics and clinical characteristics of patients with COPD.

Characteristics	All patients (<i>n</i> = 330)	COPD patients		<i>p</i> -value
		Without OSA (<i>n</i> = 234)	With OSA (<i>n</i> = 96)	
Gender				0.289
Male, <i>n</i> (%)	279 (84.5%)	201 (85.9%)	78 (81.2%)	
Female, <i>n</i> (%)	51 (15.5%)	33 (14.1%)	18 (18.8%)	
Age, years	70.0 (65.0, 77.0)	69.0 (65.0, 77.0)	71.5 (64.5, 77.5)	0.177
BMI, kg/m ²	20.25 (17.70, 24.20)	18.90 (17.30, 22.70)	24.35 (21.55, 28.63)	<0.001*
NC, cm	36 (34, 40)	34 (34, 38)	40 (38, 42)	<0.001*
Smoke				0.305
Yes, <i>n</i> (%)	267 (80.9%)	186 (79.5%)	81 (84.4%)	
No, <i>n</i> (%)	63 (19.1%)	48 (20.5%)	15 (15.6%)	
AE in the previous year				<0.001*
Yes, <i>n</i> (%)	240 (72.7%)	186 (79.5%)	54 (56.2%)	
No, <i>n</i> (%)	90 (27.3%)	48 (20.5%)	42 (43.8%)	
Hypertension				<0.001*
Yes, <i>n</i> (%)	174 (52.7%)	105 (44.9%)	69 (71.9%)	
No, <i>n</i> (%)	156 (47.3%)	129 (55.1%)	27 (28.1%)	
Type 2 diabetes				<0.001*
Yes, <i>n</i> (%)	170 (51.5%)	105 (44.9%)	65 (67.7%)	
No, <i>n</i> (%)	160 (48.5%)	129 (55.1%)	31 (32.3%)	
Coronary heart disease				<0.001*
Yes, <i>n</i> (%)	66 (20.0%)	33 (14.1%)	33 (34.4%)	
No, <i>n</i> (%)	264 (80.0%)	201 (85.9%)	63 (65.6%)	
Hyperlipidemia				0.104
Yes, <i>n</i> (%)	166 (50.3%)	111 (47.4%)	55 (57.3%)	
No, <i>n</i> (%)	164 (49.7%)	123 (52.6%)	41 (42.7%)	
Routine blood test				
WBC, × 10 ⁹ /L	7.06 (5.29, 10.30)	7.06 (5.29, 10.76)	7.04 (5.19, 8.64)	0.144
RBC, × 10 ¹² /L	4.39 (4.12, 4.81)	4.39 (4.07, 4.75)	4.40 (4.20, 4.93)	0.088
Hb, g/L	135.0 (122.8, 141.0)	135.0 (121.0, 141.0)	135.0 (123.0, 144.5)	0.833
HCT, %	41.60 (38.10, 44.70)	40.80 (37.80, 44.53)	42.20 (38.30, 45.30)	0.203
MCV, fl	92.00 (89.58, 97.30)	92.00 (89.48, 96.78)	92.50 (89.93, 99.25)	0.528
MCH, pg	30.20 (28.80, 31.90)	30.20 (28.80, 31.90)	29.80 (28.50, 31.58)	0.466
MCHC, g/L	323.0 (313.0, 332.0)	324.0 (313.0, 331.0)	319.0 (312.0, 333.5)	0.240
Coagulation index				
D-Dimer, ug/mL	0.79 (0.42, 2.03)	0.78 (0.42, 2.21)	0.79 (0.43, 1.43)	0.379
PT, s	13.7 (13.3, 14.7)	13.7 (13.1, 14.7)	13.9 (13.3, 15.3)	0.269
INR	1.08 (1.03, 1.26)	1.07 (1.01, 1.20)	1.13 (1.05, 1.28)	0.064
APTT, s	36.1 (32.9, 39.2)	36.0 (32.8, 38.8)	36.3 (33.5, 40.9)	0.023*
FIB, g/L	4.20 (3.19, 5.49)	4.26 (3.20, 5.80)	4.19 (3.17, 4.83)	0.025*
TT, s	18.20 (17.00, 19.73)	18.50 (17.20, 19.80)	17.75 (16.40, 19.10)	0.017*

(Continued)

TABLE 1 (Continued)

Characteristics	All patients (<i>n</i> = 330)	COPD patients		<i>p</i> -value
		Without OSA (<i>n</i> = 234)	With OSA (<i>n</i> = 96)	
Blood gas analysis				
PH	7.39 (7.32, 7.44)	7.39 (7.34, 7.44)	7.37 (7.29, 7.45)	0.073
PaO ₂ , mmHg	78.0 (64.0, 90.0)	77.7 (63.5, 93.0)	78.0 (64.0, 86.0)	0.793
PaCO ₂ , mmHg	46.70 (39.30, 66.40)	46.40 (39.00, 62.85)	50.40 (40.00, 71.80)	0.265
BNP, pg/mL	112.2 (57.0, 292.4)	128.1 (57.0, 350.5)	81.1 (57.0, 274.6)	0.317
CRP, mg/L	21.20 (4.79, 53.08)	24.40 (5.70, 73.61)	11.71 (3.90, 33.12)	<0.001*
Questionnaires				
mMRC, point	3 (2, 4)	3 (3, 4)	3 (2, 4)	<0.001*
CAT, point	26 (21, 31)	26 (23, 31)	21 (15, 27)	<0.001*
SACS, point	4.00 (3.00, 13.00)	3.00 (2.00, 6.00)	16.00 (8.25, 28.75)	<0.001*
mESS, point	10.00 (7.00, 14.00)	10.00 (7.00, 13.00)	9.50 (5.00, 14.75)	0.532
PSQI, point	9.00 (6.00, 12.00)	9.00 (6.00, 12.00)	9.00 (6.25, 11.00)	0.722
GOLD stage, <i>n</i> (%)				<0.001*
1	119 (36.1%)	82 (35.1%)	37 (38.5%)	
2	90 (27.3%)	60 (25.6%)	30 (31.3%)	
3	85 (25.7%)	62 (26.5%)	23 (23.9%)	
4	36 (10.9%)	30 (12.8%)	6 (6.3%)	
Sleep parameters				
AHI, times per hr	6.60 (0.60, 18.30)	1.20 (0.60, 2.30)	18.10 (12.48, 33.15)	<0.001*
ODI, times per hr	10.9 (1.3, 21.2)	1.6 (0.7, 2.9)	22.5 (18.2, 54.3)	<0.001*
Mean SaO ₂ , %	91.0 ± 3.7	92.7 ± 7.7	89.2 ± 4.6	<0.001*
Minimum SaO ₂ , %	75.2 ± 10.6	83.5 ± 6.9	72.03 ± 11.2	<0.001*

COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea syndrome; BMI, body mass index; NC, neck circumference; AE: acute exacerbation; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PT, prothrombin time; INR, international normalized ratio; APTT, activated coagulation time of whole blood; FIB, fibrinogen; TT, thrombin time; PH, potential of hydrogen; PaO₂, arterial oxygen partial pressure; PaCO₂, arterial carbon dioxide pressure; BNP, brain natriuretic peptide; CRP, C-reactive protein; mMRC, modified Medical Research Council dyspnea scale; CAT, chronic obstructive pulmonary disease assessment test; SACS, sleep apnea clinical scale; mESS, modified Epworth sleepiness scale; PSQI, Pittsburgh Sleep Quality Index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; SaO₂, arterial oxygen saturation. * Means *p* < 0.05, the difference is statistically significant.

Statistical analysis

SPSS statistical software (version 26.0, Chicago, IL, USA) and R software (version 4.2.1, <http://www.Rproject.org>) were used for analyses. Normally distributed continuous variables were represented by the mean ± standard deviation (SD), while non-normal continuous variables were expressed as the median (interquartile ranges). Categorical variables were reported as frequencies (percentages). Student's *t*-test, the Mann-Whitney U-test, the chi-square test, or Fisher's exact test were used where appropriate.

The "base" package of R was applied to randomly assign the patients to the training group and the validation group in the 7:3 ratio. In the training group, variables with a *p* < 0.05 in the univariate analysis were included in the multivariate logistic regression analysis, and the forward stepwise likelihood-ratio method was used to select the variables that were eventually included in the model. The method least absolute shrinkage

and selection operator (LASSO) was performed by using the "glmnet" R package to eliminate highly correlated factors to ensure that the multivariable logistic regression model was not overfitting. In this study, the LASSO regression was only used to ensure that the multivariable logistic regression models were not overfitting rather than for variable selection and modeling. A nomogram of the risk-predictive model for OSA was developed from the regression purposeful variable by the "rms" package in R. Candidates in the validation group were used for assessing the discrimination and calibration of the nomogram. We conducted internal validation by bootstrapping using 1,000 replications to decrease the overfit bias, then the receiver operating characteristic (ROC) curve was constructed, and the area under the ROC curve (AUC) was employed to assess the model's discrimination. Calibration curves were plotted to assess the calibration of this model, accompanied by the Hosmer-Lemeshow test (*p* > 0.05 was considered as the goodness of calibration). Decision curve analysis (DCA) shows the standardized

TABLE 2 Demographics and clinical characteristics of the training group and the validation group.

Characteristics	Training group (n = 230)			Validation group (n = 100)		
	without OSA (n = 163)	with OSA (n = 67)	p-value	without OSA (n = 71)	with OSA (n = 29)	p-value
Gender			0.203			0.970
Male, n (%)	140 (85.9%)	53 (79.1%)		61 (85.9%)	25 (86.2%)	
Female, n (%)	23 (14.1%)	14 (20.9%)		10 (14.1%)	4 (13.8%)	
Age, years	68 (64, 76)	72 (68, 78)	0.013*	71 (65, 79)	68.0 (57.5, 74.0)	0.200
BMI, kg/m ²	18.9 (17.3, 22.1)	24.3 (21.7, 28.7)	<0.001*	18.8 (17.6, 23.0)	24.4 (20.2, 26.8)	<0.001*
NC, cm	34 (34, 38)	42 (38, 44)	<0.001*	36 (34, 38)	38 (38,42)	<0.001*
Smoke			0.503			0.396
Yes, n (%)	130 (80.0%)	56 (83.6%)		56 (78.9%)	25 (86.2%)	
No, n (%)	33(20.0%)	11 (16.4%)		15 (21.1%)	4 (13.8%)	
AE in the previous year			0.007*			<0.001*
Yes, n (%)	128 (78.5%)	41 (61.2%)		58 (81.7%)	13 (44.8%)	
No, n (%)	35 (21.5%)	26 (38.8%)		13 (18.3%)	16 (55.2%)	
Hypertension			<0.001*			0.028*
Yes, n (%)	78 (47.9%)	51 (76.1%)		27 (38.0%)	18 (62.1%)	
No, n (%)	85 (52.1%)	16 (23.9%)		44 (62.0%)	11 (37.9%)	
Type 2 diabetes			0.002*			0.035*
Yes, n (%)	75 (46.0%)	46 (68.7%)		30 (42.3%)	19 (65.5%)	
No, n (%)	88 (56.0%)	21 (31.3%)		41 (57.7%)	10 (34.5%)	
Coronary heart disease			0.001*			0.016*
Yes, n (%)	20 (12.3%)	21 (31.3%)		13 (18.3%)	12 (41.4%)	
No, n (%)	143 (87.7%)	46 (68.7%)		58 (81.7%)	17 (58.6%)	
Hyperlipidemia			0.175			0.364
Yes, n (%)	74 (45.4%)	37 (55.2%)		37 (52.1%)	18 (62.1%)	
No, n (%)	89 (54.6%)	30(44.8%)		34 (47.9%)	11 (37.9%)	
Routine blood test						
WBC, × 10 ⁹ /L	7.06 (5.28, 10.69)	6.92 (5.19, 8.64)	0.273	7.79 (5.38, 11.49)	7.58 (5.39, 8.87)	0.335
RBC, × 10 ¹² /L	4.40 (4.07, 4.74)	4.39 (4.20, 4.93)	0.251	4.35 (4.03, 4.80)	4.58 (4.26, 5.16)	0.194
Hb, g/L	135 (123, 141)	134 (123, 143)	0.586	135 (119, 141)	136 (123, 152)	0.236
HCT, %	40.8 (38.2, 44.5)	42.2 (38.2, 45.0)	0.592	40.4 (36.4, 44.6)	41.9 (38.4, 46.5)	0.132
MCV, fl	92.0 (89.6, 97.0)	92.5 (89.9, 100.6)	0.698	91.7 (88.2, 96.7)	92.5 (90.4, 96.9)	0.533
MCH, pg	30.2 (28.8, 31.9)	29.6 (28.5, 31.1)	0.189	30.2 (28.8, 32.2)	30.9 (28.4, 32.0)	0.556
MCHC, g/L	325.0 (314.0, 333.0)	318.0 (312.0, 332.0)	0.076	324.0 (313.0, 330.0)	322.0 (312.5, 339.5)	0.659
Coagulation index						
D-Dimer, ug/mL	1.06 (0.42, 2.39)	0.81 (0.47, 1.61)	0.716	0.57 (0.46, 1.95)	0.75 (0.36, 1.33)	0.334
PT, s	13.7 (13.3, 14.7)	13.9 (13.3, 15.6)	0.182	13.7 (12.8, 15.0)	13.7 (13.2, 14.5)	0.897
INR	1.07 (1.03, 1.20)	1.09 (1.05, 1.28)	0.193	1.09 (0.99, 1.28)	1.15 (1.07, 1.27)	0.197
APTT, s	36.0 (32.8, 39.1)	36.3 (34.7, 39.6)	0.087	35.1 (33.0, 37.9)	37.4 (32.9, 41.7)	0.141
FIB, g/L	4.33 (3.23, 5.80)	4.19 (3.17, 4.78)	0.029*	4.03 (3.10, 6.07)	4.20 (3.11, 5.00)	0.466
TT, s	18.4 (17.1, 19.8)	17.6 (16.4, 19.4)	0.038*	18.6 (17.3, 19.8)	17.8 (17.3, 18.9)	0.189

(Continued)

TABLE 2 (Continued)

Characteristics	Training group (n = 230)			Validation group (n = 100)		
	without OSA (n = 163)	with OSA (n = 67)	p-value	without OSA (n = 71)	with OSA (n = 29)	p-value
Blood gas analysis						
PH	7.39 (7.34, 7.44)	7.37 (7.29, 7.45)	0.178	7.39 (7.35, 7.44)	7.37 (7.30, 7.45)	0.200
PaO ₂ , mmHg	77.4 (62.0, 92.0)	78.0 (64.0, 87.0)	0.797	80.0 (64.0, 95.0)	78.0 (63.5, 86.0)	0.362
PaCO ₂ , mmHg	46.4 (38.1, 65.7)	52.7 (40.0, 71.8)	0.338	45.4 (39.3, 61.9)	46.7 (39.1, 70.8)	0.608
BNP, pg/mL	120.5 (57.0, 292.4)	107.4 (55.1, 292.4)	0.803	135.9 (57.0, 352.4)	64.5 (57.8, 173.4)	0.177
CRP, mg/L	24.40 (6.27, 73.61)	10.98 (3.90, 23.88)	<0.001*	23.88 (2.52, 89.40)	12.43 (4.34, 34.70)	<0.001*
Questionnaires						
mMRC, point	3 (3, 4)	3 (2, 4)	0.007*	3 (3, 4)	3 (2, 3)	0.005*
CAT, point	26 (23, 32)	22 (17, 27)	<0.001*	26 (23, 31)	20 (15, 28)	0.001*
SACS, point	3 (2, 6)	18 (9, 30)	<0.001*	3 (2, 6)	16 (7, 18)	<0.001*
mESS, point	11 (8, 14)	10 (5, 15)	0.607	10 (6, 13)	9 (5, 15)	0.766
PSQI, point	8 (6, 12)	9 (7, 11)	0.521	9 (6, 12)	9 (6, 11)	0.771
GOLD Stage, n (%)			<0.001*			<0.001*
1	57 (35.0%)	25 (37.3%)		26 (36.6%)	7 (24.1%)	
2	45 (27.6%)	20 (29.8%)		13 (18.3%)	11 (37.9%)	
3	43 (26.4%)	17 (25.4%)		19 (26.8%)	7 (24.1%)	
4	18 (11.0%)	5 (7.5%)		13 (18.3%)	4 (13.9%)	
Sleep parameters						
AHI (times per hr)	1.1 (0.3, 2.5)	12.6 (6.3, 17.8)	<0.001*	1.2 (0.4, 2.7)	14.2 (8.1, 19.8)	<0.001*
ODI (times per hr)	1.6 (0.6, 3.5)	41.2 (18.13, 63.5)	<0.001*	1.8 (0.7, 3.5)	38.2 (18.2, 63.0)	<0.001*
Mean SaO ₂ (%)	95.6 ± 2.2	93.7 ± 3.4	<0.001*	94.9 ± 4.2	91.4 ± 3.0	<0.001*
Minimum SaO ₂ (%)	87.50 ± 7.70	71.33 ± 11.32	<0.001*	87.60 ± 4.81	73.66 ± 10.89	<0.001*

COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea syndrome; BMI, body mass index; NC, neck circumference; AE: acute exacerbation; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PT, prothrombin time; INR, international normalized ratio; APTT, activated coagulation time of whole blood; FIB, fibrinogen; TT, thrombin time; PH, potential of hydrogen; PaO₂, arterial oxygen partial pressure; PaCO₂, arterial carbon dioxide pressure; BNP, brain natriuretic peptide; CRP, C-reactive protein; mMRC, modified Medical Research Council dyspnea scale; CAT, chronic obstructive pulmonary disease assessment test; SACS, sleep apnea clinical scale; mESS, modified Epworth sleepiness scale; PSQI, Pittsburgh Sleep Quality Index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; SaO₂, arterial oxygen saturation.

net benefit relative to the risk threshold probability and is used to evaluate the clinical utility of the model (Fitzgerald et al., 2015). The clinical impact curve analysis (CICA) shows the number of high-risk and true-positive patients at different threshold probabilities. A two-sided $p < 0.05$ was considered to be statistically significant.

Results

Characteristics of patients

We recruited 338 patients initially. A total of eight patients were excluded for the following reasons: those who refused overnight sleep tests ($n = 3$), those who have received NPPV therapies before ($n = 1$), those who are pregnant ($n = 1$), and those who have incomplete clinical data ($n = 3$). A total of 96

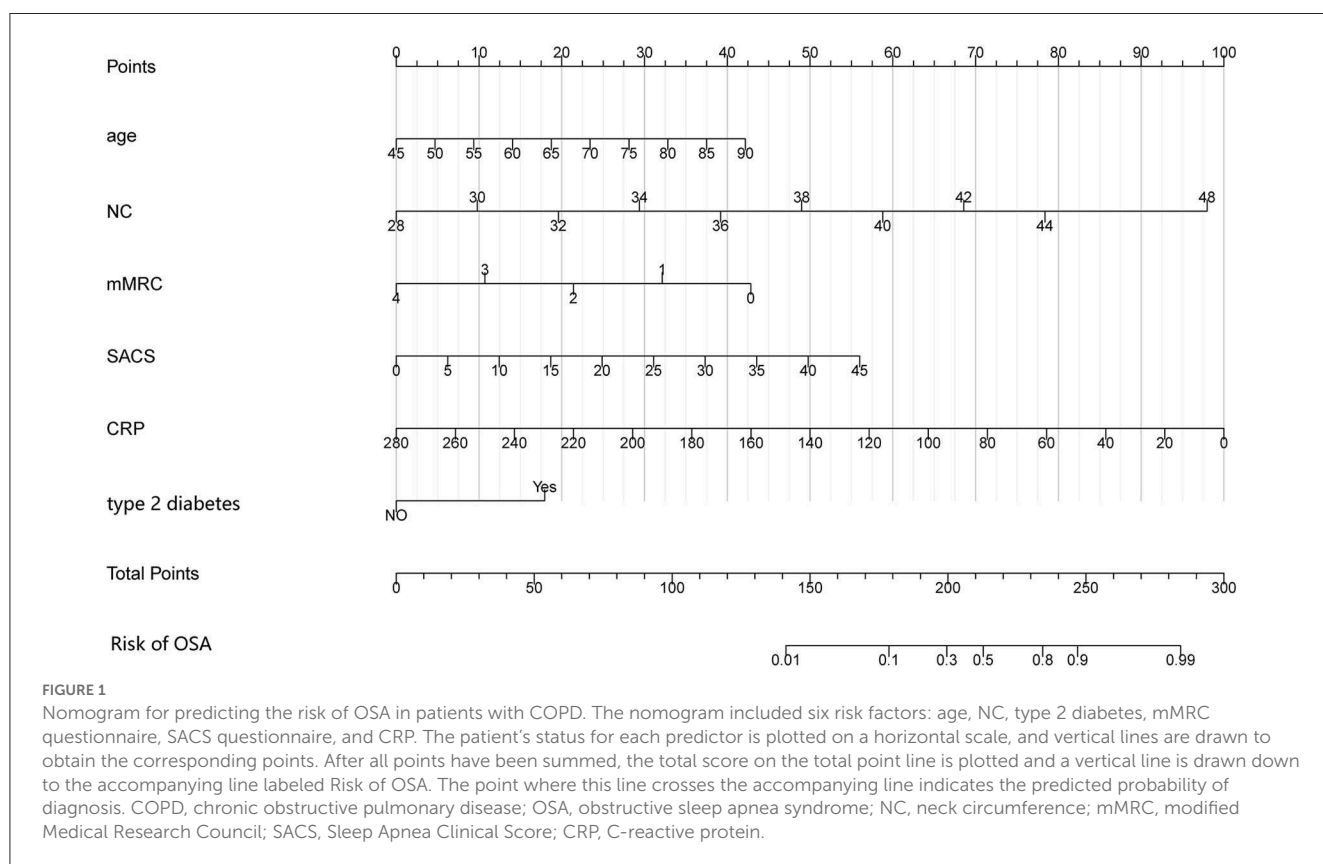
(29.1%) patients were diagnosed with OSA with a median age of 70 years. A total of 279 (84.5%) participants were men, 267 (80.9%) had a smoking history, and the common comorbidities among patients were hypertension (52.7%), type 2 diabetes (51.5%), coronary heart disease (20.0%), and hyperlipidemia (50.3%). As compared with patients with COPD alone, patients with COPD combined with OSA were overweight, had poorer sleep quality, less acute exacerbation (AE) of COPD in the prior year, more underlying diseases, but lower C-reactive protein (CRP) and better airway obstruction (all $p < 0.05$). A detailed comparison of clinical data between with and without OSA groups is shown in Table 1.

A total of 230 participants were randomly assigned to the training group and 100 to the validation group. Across the training and validation groups, 79.1 and 86.2% of patients with OSA, respectively, were men. In the training group, 67 (29.1%) patients were diagnosed with OSA, with a median age of 72 years. In the

TABLE 3 Multivariate logistic regression analysis in train group.

Variable	β coefficient	Standard error	Wald	OR (95%CI)	p-value
Age	0.060	0.029	4.314	1.062 (1.003–1.124)	0.038
Type 2 diabetes	1.153	0.469	6.038	3.166 (1.263–7.939)	0.014
NC	0.315	0.113	7.761	1.370 (1.098–1.709)	0.005
mMRC	−0.688	0.222	9.578	0.503 (0.325–0.777)	0.002
SACS	0.080	0.039	4.299	1.083 (1.004–1.168)	0.038
CRP	−0.023	0.008	7.861	0.977 (0.962–0.993)	0.005
Constants	−16.016	4.488	12.735	0.000	<0.001

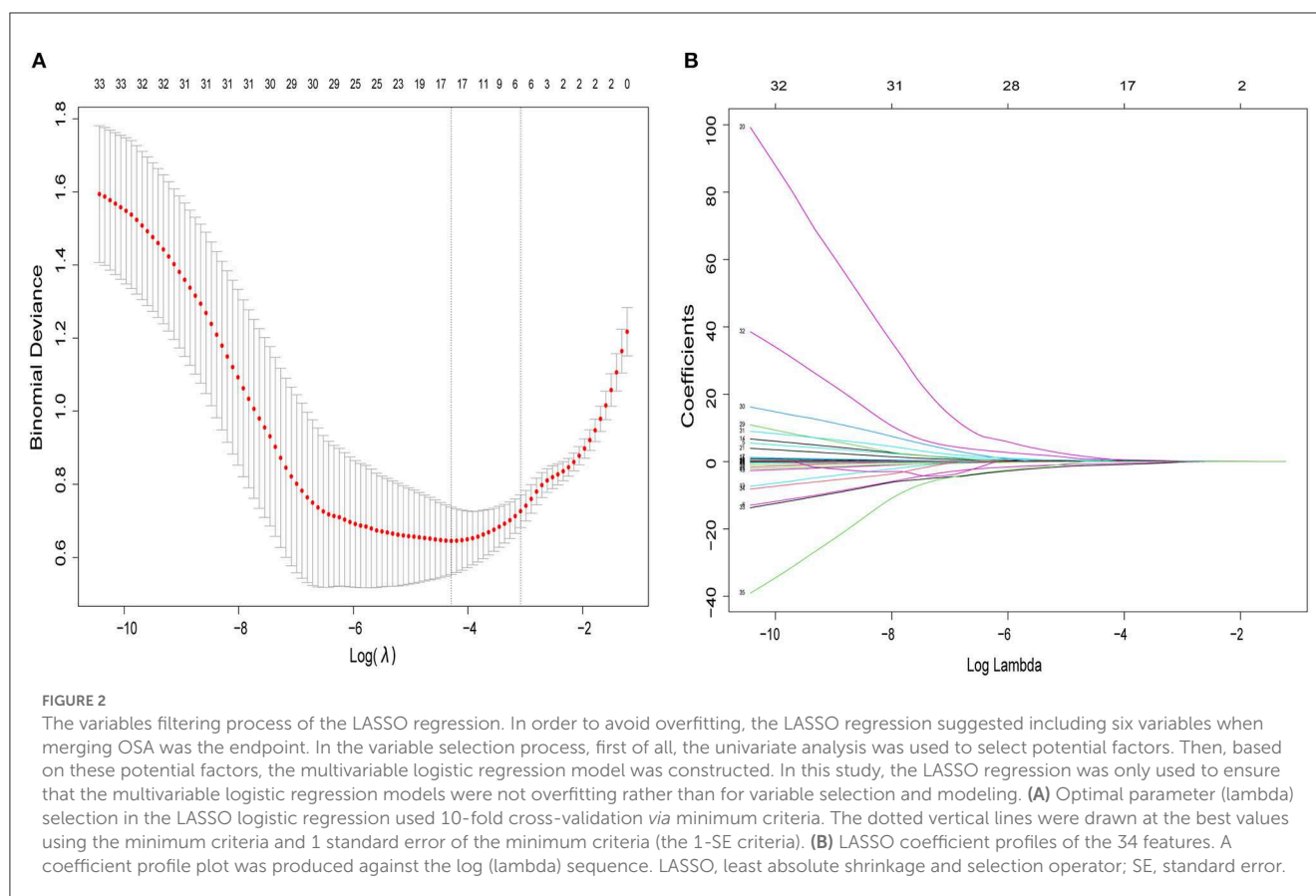
CI, confidence interval; OR, odds ratio; NC, neck circumference; mMRC, modified Medical Research Council dyspnea scale; SACS, sleep apnea clinical scale; CRP, C-reactive protein. *Means $p < 0.05$, the difference is statistically significant.



validation group, 29 (29.0%) patients were diagnosed with OSA, with a median age of 68 years. There were no significant differences in the features of demographic and clinical characteristics between training and validation groups (Supplementary Table 1). Table 2 summarizes the characteristics of patients with COPD with and without OSA of the training group and the validation group. Patients in both OSA groups revealed a higher proportion of hypertension, type 2 diabetes, and coronary heart disease; higher BMI, NC, SACS; lower CRP, mMRC, and CAT; as well as poorer polysomnographic data and less AE (all $p < 0.05$). The differences in airflow limitation between OS and COPD groups in training and validation groups were statistically significant ($p < 0.05$). Participants who experienced more AE showed worse airflow limitation and poorer health status.

Construction of the nomogram

The multivariate logistic regression model considered 14 parameters with a $p < 0.05$ in the univariate analysis, including age, BMI, NC, hypertension, type 2 diabetes, coronary heart disease, AE in the previous year, fibrinogen, thrombin time, CRP, mMRC, CAT, SACS, and GOLD stage. The multivariate logistic analysis showed six independent risk-predictive factors for OS to develop nomogram: age (OR: 1.062, 1.003–1.124), type 2 diabetes (OR: 3.166, 1.263–7.939), NC (OR: 1.370, 1.098–1.709), mMRC (OR: 0.503, 0.325–0.777), SACS (OR: 1.083, 1.004–1.168), and CRP (OR: 0.977, 0.962–0.993) (Table 3, Figure 1). All variables eventually incorporated into the multivariate model were essential to the modeling process in the LASSO regression (Figure 2). LASSO



regression minimized the influence of multicollinearity and had the advantages of strong predictability and high robustness. We identified independent factors in the training group by non-zero coefficients in the LASSO regression, and optimal parameter (lambda) selection in the LASSO model used 10-fold cross-validation *via* minimum criteria.

Validation of the nomogram

The validation of the nomogram was performed with a 1,000 bootstrap analysis. The nomogram yielded relatively high AUCs in both the training group [0.929, 95% confidence interval (CI) 0.894–0.965] and validation group (0.928, 95%CI 0.873–0.984), exceeding 0.7 in both cases, indicating a satisfactory performance (Figure 3A). Moreover, observations and predictions of OS correlated well with the calibration plots (Figures 3B, C). The Hosmer–Lemeshow test also showed that there was no significant statistical difference in both the training group ($\chi^2 = 13.552$, $p = 0.139$) and the validation group ($\chi^2 = 10.710$, $p = 0.296$), suggesting that the nomogram was well-calibrated.

Clinical application

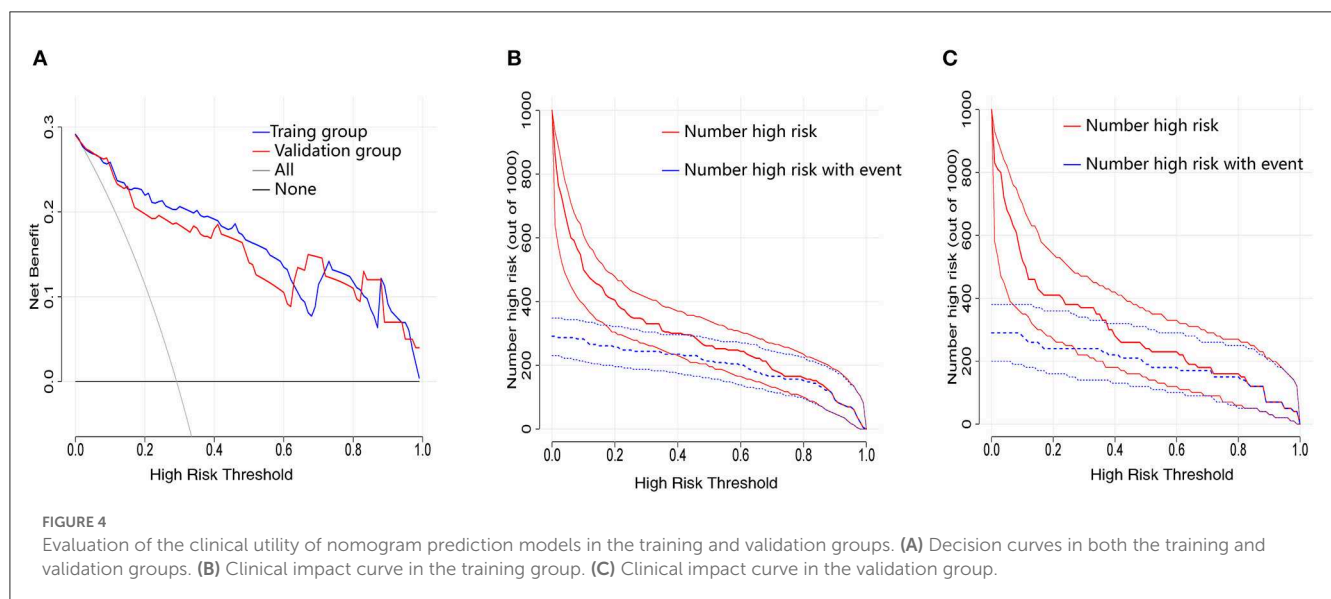
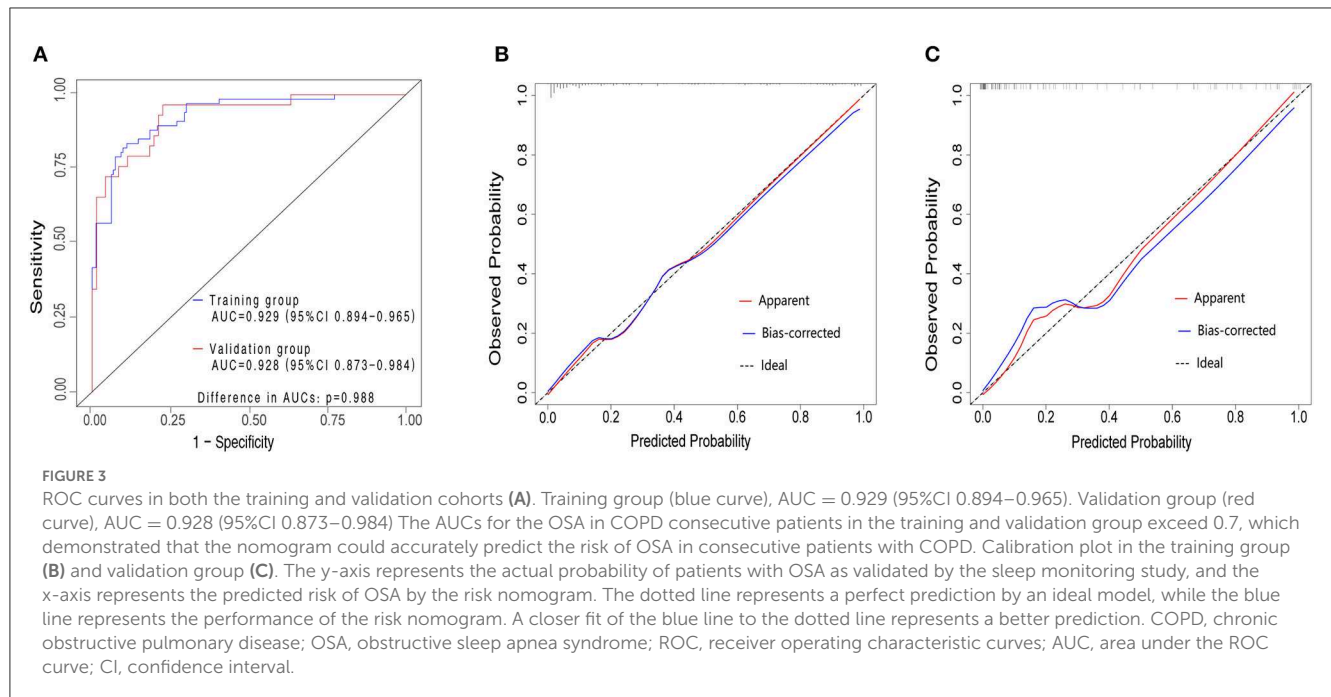
Decision curve analysis is a method to assess the benefits of a diagnostic test by quantifying the net benefit at different threshold probabilities to determine the clinical usefulness of the

nomogram. Compared to the two thresholds of “no intervention” and “intervention for all,” both the training and validation groups displayed higher clinical net benefit (Figure 4A). The clinical impact curves for the training group (Figure 4B) and the validation group (Figure 4C) also showed good predictability and clinical utility.

Discussion

Currently, OSA in the context of COPD is common with little attention. The prevalence of COPD combined with OSA varies from 2.9 to 65.9% (Shawon et al., 2017), and there is increasing evidence that patients with COPD are more likely to suffer from OSA than the general population of the same age (Sacks et al., 2018; Zhang et al., 2022). COPD patients with OSA tend to have more basic diseases and higher mortality than COPD-only patients, but the costly and time-consuming PSG and the possible bias of questionnaires may lead to underdiagnosis. Therefore, it is important to predict and diagnose OSA early. This study revealed the incidence of OSA as well as the risk factors for developing OSA. These terms are readily available and have good predictive performance, which is suitable for use in outpatients and hospitals without PSG. Our nomogram shows good discrimination and sufficient prediction performance, therefore, proving it to be robust.

We observed that of the 330 patients with COPD, the prevalence of OSA was 29.1%, which was at a relatively moderate level. Compared with patients with COPD alone, patients



combined with OSA were overweight, had lower CRP, better airway obstruction, and less AE during the 12 months before enrolling into the study, and were more likely to have type 2 diabetes. It has been reported in the literature that OSA is very common in patients with type 2 diabetes, 55–86% of whom have OSA (Schipper et al., 2021). Obstructive sleep apnea syndrome, through the effects of intermittent hypoxemia and sleep fragmentation, could contribute to the development of type 2 diabetes (Aurora and Punjabi, 2013). Meanwhile, age and obesity are well-known predictors of OSA. Studies revealed that the incidence of OSA was positively correlated with age (Fietze et al., 2019; Lyons et al., 2020). Older adults might have reduced tethering of the upper airway by lung volume because of loss of elastic recoil in the lung or have a more easily collapsible airway caused by the loss of collagen. Moreover, the efficiency of the upper airway dilator muscles might fall with age (Eikermann

et al., 2007; Liu et al., 2021). Body mass index, as an indicator of obesity, reflects overall fat distribution but does not adequately take into account neck fat distribution, which has limitations. Obesity could increase the likelihood of airway collapse by directly affecting the anatomy of the upper airway as fat is deposited in the neck (Schwartz et al., 2010; McNicholas and Pevernagie, 2022). Some studies showed that neck fat is thicker in OSA than in non-apnea snorers (Morinigo et al., 2022). Therefore, compared with traditional obesity evaluation, such as BMI, NC is a more accurate independent predictor of OSA (Simpson et al., 2010; Cho et al., 2016; Gasa et al., 2019).

In patients with COPD, an increase in breathing as a result of small (<2 mm) airway obstruction, muscle contraction, and elastic recoil of the lung instigate symptoms of dyspnea (Rabe, 2006; O'Donnell et al., 2007). A review proposed the “obesity paradox”

and speculated its possible mechanism, which concluded that obese patients with COPD have better dyspnea scores than non-obese patients (Guenette et al., 2010). Furthermore, the prevalence of OSA has gradually increased with the epidemic of obesity according to epidemiological data (Young et al., 1993; Peppard et al., 2013); that is, non-obese patients with COPD have more severe dyspnea but a lower probability of combined OSA than obese patients. This is consistent with the results from our study where patients with COPD alone have higher mMRC scores. This parameter can be used as an independent factor and diagnostic criterium of OSA.

C-reactive protein has been proven to be an effective inflammatory biomarker during COPD exacerbation. It was reported that CRP concentrations were found to be consistently elevated in the AE state and were significantly higher than in healthy or stable controls (Valipour et al., 2008; Lin et al., 2019). Meanwhile, a high level of CRP was related to the risk of AE (Cano et al., 2004; Thomsen et al., 2013). It is valuable in the confirmation of COPD exacerbation when combined with a major exacerbation symptom (Hurst et al., 2006). This is consistent with our results that CRP was inversely correlated with the incidence of OSA. Notably, patients with COPD alone had more AE in the prior year in our research though some reports held opposite opinions (Marin et al., 2010; Donovan et al., 2019; Hong et al., 2020). The reason for this phenomenon is possibly that patients with COPD in our study were with an AE state and had lower BMI (median:18.90), compared with patients with COPD from Western countries (the median BMI of most patients with COPD is ≥ 25 kg/m²). The loss of body weight is a common problem in patients with COPD (Engelen et al., 1994, 1999). BMI was correlated with pulmonary function positively and exacerbations negatively (Cano et al., 2004; Wu et al., 2018). However, studies should be more and deeper to verify our results.

Among the available screening tools for detecting OSA, although these questionnaires were validated in the general population, they were found to have limited sensitivity and specificity in specific populations. Xiong et al., in a 2019 study on five questionnaires in screening COPD patients with OSA showed that SACS had a moderate predictive value in screening severe OSA, with an AUC of 0.750 (Xiong et al., 2019). While Wang et al. (2021) showed that SACS had excellent sensitivity (93.4–94.6%) and a negative predictive value (77.3–90.9%) in evaluating the prevalence of OSA in patients with COPD. In our study, SACS has a good predictive value, but there are few studies on the predictive value of SACS in COPD patients with OSA, and more studies are still needed.

We construct a nomogram in which all predictors are common demographic and anthropometry measures and questionnaires that could be obtained in outpatient without additional testing, greatly reducing the burden on physicians and patients, and facilitating the clinical procedure for OS diagnosis. There are some limitations to this study. First, this is a single-center study, where training and validation groups are recruited from the same center. Multicenter studies should be developed to validate our results. Second, our samples are relatively small. Third, we used the PM device. However, previous studies (Parra et al., 1997; Vat et al., 2015) showed good consistency and correlation between the PM device and PSG results.

In conclusion, we developed and validated a new nomogram model, which consisted of six independent risk factors for OSA, which may empower clinicians and patients with COPD with earlier, more accurate information regarding the risk of OSA.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology. The patients/participants provided their written informed consent to participate in this study.

Author contributions

TP, WW, SY, and JZ conceived and designed the study. TP, WW, and SY collected the data. TP, ZL, YY, ZH, and RN participated in the investigation of the study. TP analyzed the data. TP and JZ were responsible for data interpretation. TP, WW, AJ, XW, and JZ wrote the initial draft of the manuscript. SY, ZL, YY, ZH, and RN involved in revising the manuscript. All authors contributed to the study and also read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnins.2023.1146424/full#supplementary-material>

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