Nature and Science of Sleep

Elevate Series

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ORIGINAL RESEARCH

Construction and Validation of a Nomogram Model for Predicting Pulmonary Hypertension in Patients with Obstructive Sleep Apnea

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Purpose: Pulmonary hypertension (PH) is a common cardiovascular complication of obstructive sleep apnea (OSA), posing a significant threat to the health and life of patients with OSA. However, no clinical prediction model is currently available to evaluate the risk of PH in OSA patients. This study aimed to develop and validate a nomogram for predicting PH risk in OSA patients.

Patients and Methods: We collected medical records of OSA patients diagnosed by polysomnography (PSG) from January 2016 to June 2024. Transthoracic echocardiography (TTE) was performed to evaluate PH. A total of 511 OSA patients were randomly divided into training and validation sets for model development and validation. Potential predictive factors were initially screened using univariate logistic regression and Lasso regression. Independent predictive factors for PH risk were identified via multivariate logistic regression, and a nomogram model was constructed. Model performance was assessed in terms of discrimination, calibration, and clinical applicability.

Results: Eight independent predictive factors were identified: age, recent pulmonary infection, coronary atherosclerotic heart disease (CHD), apnea-hypopnea index (AHI), mean arterial oxygen saturation ($MSaO_2$), lowest arterial oxygen saturation ($LSaO_2$), alpha-hydroxybutyrate dehydrogenase (α-HBDH), and fibrinogen (FIB). The nomogram model demonstrated good discriminative ability (AUC = 0.867 in the training set, AUC = 0.849 in the validation set). Calibration curves and decision curve analysis (DCA) also indicated good performance. Based on this model, a web-based nomogram tool was developed.

Conclusion: We developed and validated a stable and practical web-based nomogram for predicting the probability of PH in OSA patients, aiding clinicians in identifying high-risk patients for early diagnosis and treatment.

Keywords: obstructive sleep apnea, pulmonary hypertension, clinical prediction model, nomogram, risk factor

Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by recurrent upper airway obstructions during sleep, leading to intermittent hypoxia (IH), hypercapnia, oxidative stress, autonomic dysfunction, and sleep fragmentation.[1,2] It is associated with multiple complications, including cardiovascular diseases, type 2 diabetes, metabolic disorders, and cognitive impairments.[3,4] With the growth of the global population and economy, the prevalence of OSA is increasing. It is estimated that approximately 936 million individuals aged 30 to 69 worldwide suffer from OSA.[5] A serious threat to public health arises from the large number of misdiagnosed and untreated cases caused by low awareness of OSA. Pulmonary hypertension (PH) is a progressive disease caused by elevated pulmonary arterial pressure, leading to right heart failure and high mortality, with a 3-year survival rate of approximately 70% to 80%.[6] Its pathophysiology involves increased pulmonary vascular resistance due to vasoconstriction, thrombosis, and vascular remodeling.[7] PH is a significant global health issue, affecting all age groups, with a prevalence of 1% globally and up to 10% in individuals over 65.[8,9] Despite advancements in right heart catheterization (RHC) and targeted therapies, PH remains challenging to diagnose early and treat effectively. Recent studies have identified OSA as an independent risk factor for cardiovascular diseases, including coronary heart disease, heart failure, and PH.[10–12] PH as one of the common cardiopulmonary complications of OSA, the relationship between them has increasingly attracted attention and has become a research focus in recent years.

Received: 10 February 2025
Accepted: 23 April 2025
Published: 24 May 2025

With OSA-associated PH being classified as Group 3 PH, it suggests a direct relationship between the two diseases.[9] Numerous studies have confirmed that PH occurrence and progression are closely related to OSA, which may be an independent risk factor for PH. Related observational studies show a PH prevalence of 15%–80% in OSA patients and an OSA prevalence of 70%–80% in patients with PH diagnosed via RHC.[2,13,14] Furthermore, studies have demonstrated that OSA can worsen PH and cause right heart dysfunction, and that apnea-hypopnea index (AHI) is an independent predictor of right heart dysfunction.[15,16] The primary treatment for OSA is continuous positive airway pressure (CPAP),[17] which has demonstrated to alleviate PH in OSA patients and significantly reduces pulmonary artery systolic pressure (PASP)).[18,19] Studies suggest that OSA primarily affects the development of PH through IH, sleep fragmentation, oxidative stress, inflammation, sympathetic activation, and hypercoagulability.[20,21] Conversely, PH can exacerbate OSA by causing right heart dysfunction. Right heart dysfunction can lead to upper airway edema and reduced cardiac output, which worsens hypoxia and hypercapnia of OSA, creating a vicious cycle.[22,23] In summary, the close relationship and interaction between OSA and PH may lead to poor outcomes with monotherapy and rapid disease progression. Therefore, early risk screening for PH in OSA patients is crucial in clinical practice.

At present, PH diagnosis mainly relies on RHC and transthoracic echocardiography (TTE). Although RHC is the gold standard, TTE is widely used due to its safety, cost-effectiveness, and patient acceptance. The 2022 ESC/ERS guidelines[9] recommend the use of TTE for initial assessment and RHC for confirmation when needed, demonstrating the feasibility and priority of TTE. However, large-scale studies on OSA and PH are limited, resulting in a lack of unified treatment principles. This results in low awareness of PH among OSA patients and primary care physicians, often delaying early diagnosis and intervention, thereby allowing the disease to progress. Therefore, developing a convenient, efficient, and clinically applicable prediction model to early assess PH risk in OSA patients is essential. Current research on OSA-related PH focuses on risk factors but lacks specific clinical prediction models.[24,25] Therefore, constructing a diagnostic prediction model to predict the risk of PH in OSA patients is particularly important.

This study aims to develop a nomogram model based on existing clinical data to assess the risk of PH in OSA patients. The model helps clinicians identify high-risk PH populations among OSA patients, allowing for timely intervention and health guidance. It also raises patients' awareness of OSA-related PH, promoting active disease management by themselves. This approach can delay PH progression, reduce complications, and improve patients' prognosis.

Materials and Methods

The detailed data collection and model development process is described in Figure 1

Study Design and Subjects

This retrospective study collected medical records of patients who underwent polysomnography (PSG) and were diagnosed with OSA, with complete TTE results, at the Second Affiliated Hospital of Kunming Medical University from January 2016 to June 2024. The diagnosis of OSA was by the latest international standards, defined as an AHI of ≥5 events per hour as indicated by PSG. The diagnosis of PH was based on the 2022 ESC/ERS guidelines,[9] which uses TTE for the estimation of PASP, with a threshold of tricuspid regurgitation peak velocity >2.8 m/s, corresponding to an estimated PASP threshold of 40 mmHg, thus diagnosing PH as PASP ≥40 mmHg. The inclusion criteria were as follows: (1) patients aged ≥18 years; (2) all patients completed PSG after admission and met the diagnostic criteria for OSA; (3) patients who had not been previously diagnosed with OSA and undergone OSA-related treatment. The exclusion criteria were as follows: (1) patients with incomplete clinical records; (2) patients diagnosed with central sleep apnea (CSA) or mixed sleep apnea; (3) patients with organic heart diseases; (4) patients with chronic obstructive pulmonary disease (COPD), pulmonary interstitial fibrosis, or other chronic pulmonary diseases; (5) patients with idiopathic pulmonary arterial hypertension(IPAH) or connective tissue disease-related interstitial lung disease. This study complied with the provisions of the Helsinki Declaration, and the study design was approved by the Ethics Committee of the Second Affiliated Hospital of Kunming Medical University (approval no. 2024283), with informed consent obtained from each participating patient.

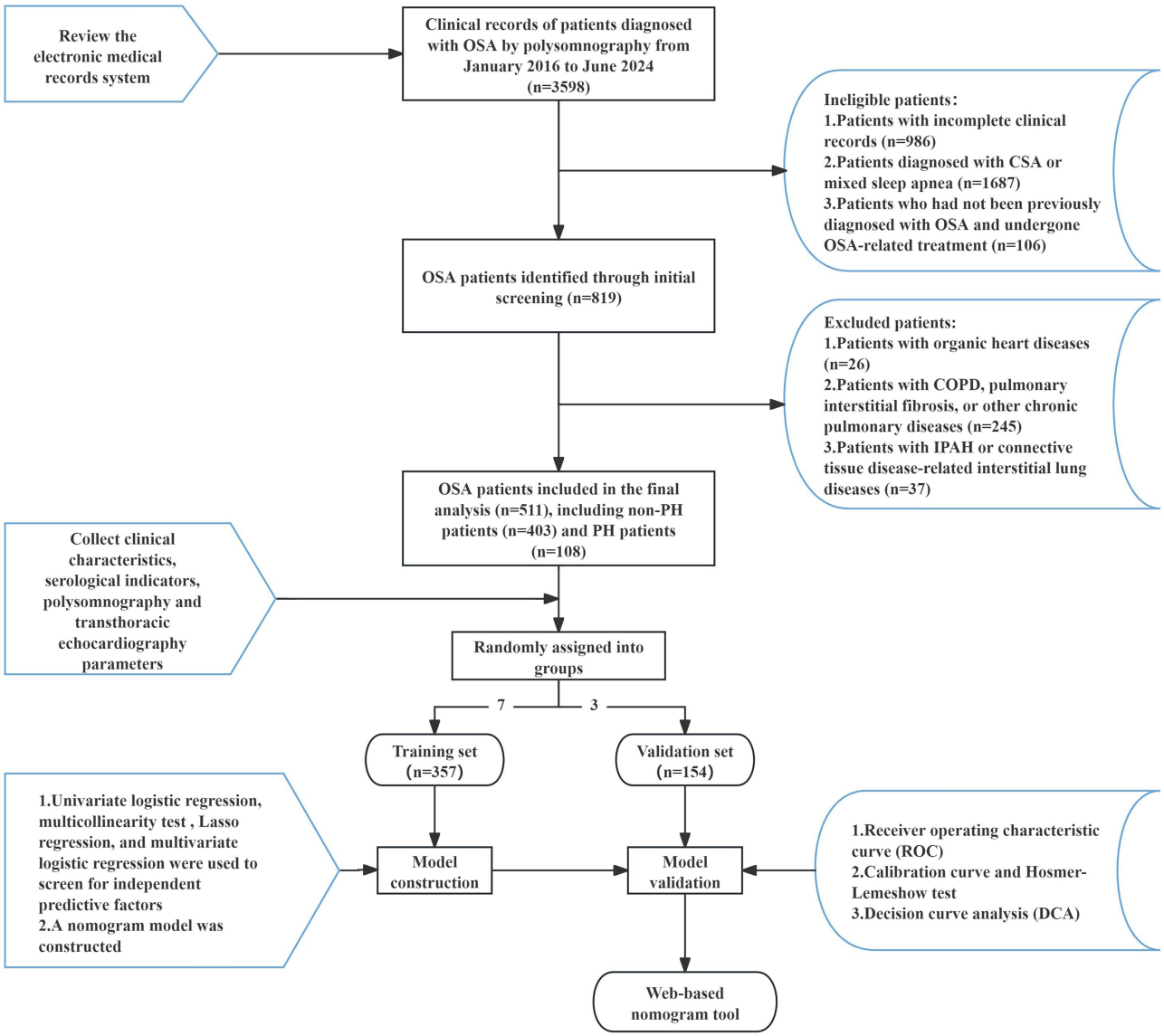

Figure 1 Flow chart.

Basic Data Collection

Anthropometric and Clinical Characteristics

Demographic data, physical examination, and co-morbidities were collected for each patient. This included gender, age, height, weight, body mass index (BMI), history of smoking, history of alcohol consumption, hypertension, type 2 diabetes mellitus (T2DM), fatty liver disease (FLD), cerebral infarction (CI), coronary atherosclerotic heart disease-(CHD), and recent pulmonary infection.

Serological Parameters

Fasting venous blood samples were collected on the morning of the day after the patients were admitted to the hospital for laboratory testing, without relevant medication before blood collection. Standard instruments and methods were used to measure and record the results of the following serological tests: (1) Complete blood count (CBC) parameters, including white blood cell count (WBC), neutrophil count (N), lymphocyte count (L), monocyte count (M), eosinophil count (E), basophil count (B), platelet count (PLT), red cell distribution width (RDW), and other CBC parameters; (2) Blood biochemical parameters, including albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase

https://doi.org/10.2147/NSS.S520758

(AST), lactate dehydrogenase (LDH), α-hydroxybutyrate dehydrogenase (α-HBDH), creatine kinase (CK), creatine kinase-MB (CK-MB), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), and other blood biochemical parameters; (3) Coagulation function parameters, including prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen (FIB), and thrombin time (TT). The following composite indicators were also calculated: neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), triglyceride-glucose (TyG) index, and systemic coagulation-inflammation index (SCI). Among these indicators, the SII combines neutrophil, platelet, and lymphocyte counts to reflect systemic immune and inflammatory status. Elevated SII levels are associated with various inflammatory conditions and serve as a prognostic marker in several diseases. The SIRI integrates neutrophil, monocyte, and lymphocyte counts to assess the systemic inflammatory response and evaluate the severity of infections and other inflammatory conditions. Lastly, the SCI incorporates platelet count, fibrinogen levels, and white blood cell count to assess the interplay between coagulation and inflammation in various clinical settings.

PSG Parameters

All patients underwent PSG during their hospitalization, and they were informed in advance of the precautions related to performing PSG to ensure the accuracy of the results. PSG began around 10:00 PM and ended after 7:00 AM the following morning, and the duration of PSG was not less than 7 hours. After the monitoring, all results were initially analyzed by the computer system and then corrected and interpreted by professional physicians to generate the final sleep monitoring report. Relevant sleep monitoring parameters were collected, including AHI, oxygen desaturation index (ODI), mean oxygen saturation ($MSaO_2$), and lowest oxygen saturation ($LSaO_2$).

TTE Parameters

All patients underwent TTE and were evaluated and reviewed by two specialized cardiac ultrasonographers to generate a final TTE report. Relevant TTE parameters were collected, including PASP, cardiac output (CO), and left ventricular ejection fraction (LVEF). According to the guidelines,[9] a threshold of tricuspid regurgitation peak velocity > 2.8 m/s was used to calculate PASP ≥ 40 mmHg as the diagnostic criterion for PH. Based on the modified Bernoulli equation, the formula for calculating PASP is: PASP = 4VTR^2 + RAP (VTR is the maximum tricuspid regurgitation velocity; RAP is the right atrial pressure, assumed to be 10 mmHg).

Statistical Analysis

Statistical analysis and graphing were performed using SPSS 27.0 and R 4.4.1 software. Continuous data were tested for normality using the Shapiro–Wilk test. Normally distributed data were presented as means ± standard deviation and compared using two independent samples *t*-tests; non-normally distributed data were presented as median (interquartile ranges) and compared using Mann–Whitney *U*-tests. Categorical data were presented as frequencies (percentages) and compared using Chi-square tests. The R "caret" package was used to randomly divide the patients into a training set (70%) and a validation set (30%) for model development and validation, respectively. In the training set, the occurrence of PH in OSA patients was used as the outcome variable. Univariate logistic regression was used to screen the related risk factors. Variables with $P < 0.05$ were further tested for multicollinearity by calculating the variance inflation factor (VIF),[26] with variables having a VIF < 10 being included in Lasso regression for further screening of characteristic variables. The predictive variables screened by Lasso were analyzed via multivariate logistic regression to construct a nomogram model. The model's discrimination was assessed using the area under the receiver operating characteristic curve (AUC-ROC), the accuracy using calibration curves and the Hosmer-Lemeshow goodness-of-fit test, and the clinical validity using decision curve analysis (DCA). Finally, a web-based nomogram was developed based on this model to facilitate clinical application. A P value < 0.05 was considered statistically significant.

Results

Basic Characteristics of the Study Population

After screening, a total of 511 subjects were included in the analysis, including 324 males (63.40%) and 187 females (36.60%). The average age of the subjects was 60.37 years old, and the average BMI was 25.89 kg/m². Among them, there were 104 patients with mild OSA, 192 patients with moderate OSA, and 215 patients with severe OSA. Based on the results of the TTE, the subjects were further divided into the non-PH group (n=403) and the PH group (n=108). Compared to the non-PH group, the patients in the PH group exhibited significant differences in several aspects: they were older on average, had a higher proportion of patients over 60 years old, had higher BMI, and had higher prevalence rates of recent pulmonary infection, previous hypertension, and coronary atherosclerotic heart disease (CHD). Additionally, patients in the PH group showed higher values for the following indicators: AHI, ODI, N, M, RDW-CV, RDW-SD, NLR, MLR, SII, SIRI, PT, INR, FIB, LDH, α-HBDH, and FBG. In contrast, the PH group showed lower values for the following indicators: $MSaO_2$, $LSaO_2$, L, HB, MCHC, PLT, ALB, ALT, TC, TG, LDL-C, Non-HDL-C, and TyG. All these differences were statistically significant ($P<0.05$; Tables 1–4).

Table 1 Anthropometric and Clinical Characteristics of the Study Participants

Variables	Total (n = 511)	Non-PH (n = 403)	PH (n = 108)	P value
Age, M (Q_1, Q_3)	59.00 (50.00, 69.00)	57.00 (48.00, 66.00)	69.00 (58.00, 76.00)	<0.001
BMI, M (Q_1, Q_3)	25.60 (22.95, 28.05)	25.39 (22.70, 27.85)	26.30 (23.37, 28.72)	0.036
Gender, n(%)				0.314
Male	324 (63.41)	260 (64.52)	64 (59.26)	
Female	187 (36.59)	143 (35.48)	44 (40.74)	
Pulmonary infection, n(%)				0.002
No	435 (85.13)	353 (87.59)	82 (75.93)	
Yes	76 (14.87)	50 (12.41)	26 (24.07)	
Hypertension, n(%)				0.001
No	207 (40.51)	178 (44.17)	29 (26.85)	
Yes	304 (59.49)	225 (55.83)	79 (73.15)	
T2DM, n(%)				0.690
No	386 (75.54)	306 (75.93)	80 (74.07)	
Yes	125 (24.46)	97 (24.07)	28 (25.93)	
FLD, n(%)				0.683
No	294 (57.53)	230 (57.07)	64 (59.26)	
Yes	217 (42.47)	173 (42.93)	44 (40.74)	
CI, n(%)				0.370
No	354 (69.28)	283 (70.22)	71 (65.74)	
Yes	157 (30.72)	120 (29.78)	37 (34.26)	
CHD, n(%)				<0.001
No	444 (86.89)	366 (90.82)	78 (72.22)	
Yes	67 (13.11)	37 (9.18)	30 (27.78)	
Smoking, n(%)				0.334
No	301 (58.90)	233 (57.82)	68 (62.96)	
Yes	210 (41.10)	170 (42.18)	40 (37.04)	
Drinking, n(%)				0.915
No	357 (69.86)	282 (69.98)	75 (69.44)	
Yes	154 (30.14)	121 (30.02)	33 (30.56)	
Age 60, n(%)				<0.001
<60	278 (54.40)	244 (60.55)	34 (31.48)	
≥60	233 (45.60)	159 (39.45)	74 (68.52)	

Notes: Mean ± SD, means ± standard deviation; M(Q_1,Q_3), median (interquartile range); n(%), number (percentage).
Abbreviations: BMI, body mass index; T2DM, type 2 diabetes mellitus; FLD, fatty liver disease; CI, cerebral infarction; CHD, coronary atherosclerotic heart disease; Age 60, age subgroups (using 60 years as the boundary).

https://doi.org/10.2147/NSS.S520758

Table 2 Complete Blood Count and Coagulation Function -Related Parameters of the Study Participants

Variables	Total (n = 511)	Non-PH (n = 403)	PH (n = 108)	P value
N, M (Q_1, Q_3)	3.72 (2.92, 4.99)	3.63 (2.83, 4.86)	4.10 (3.22, 5.49)	0.002
L, M (Q_1, Q_3)	1.94 (1.54, 2.38)	1.97 (1.57, 2.42)	1.84 (1.41, 2.27)	0.035
M, M (Q_1, Q_3)	0.42 (0.34, 0.51)	0.40 (0.33, 0.50)	0.45 (0.36, 0.54)	0.009
E, M (Q_1, Q_3)	0.13 (0.08, 0.20)	0.13 (0.08, 0.20)	0.11 (0.06, 0.19)	0.050
B, M (Q_1, Q_3)	0.03 (0.02, 0.04)	0.03 (0.02, 0.04)	0.02 (0.01, 0.04)	0.069
HB, M (Q_1, Q_3)	148.00 (137.00, 160.00)	149.00 (138.00, 160.50)	144.00 (133.00, 158.00)	0.038
HCT, M (Q_1, Q_3)	0.44 (0.41, 0.47)	0.44 (0.41, 0.47)	0.44 (0.41, 0.47)	0.198
MCV, M (Q_1, Q_3)	91.40 (88.50,94.30)	91.30 (88.40,94.15)	91.50 (89.00,94.70)	0.448
MCH, M (Q_1, Q_3)	30.60 (29.50,31.70)	30.70 (29.60,31.80)	30.40 (29.30,31.60)	0.061
MCHC,M(Q_1,Q_3)	335.00 (328.00,342.00)	336.00 (329.00,343.00)	332.00 (326.75,339.00)	<0.001
RDW-CV,M(Q_1,Q_3)	13.10 (12.70, 13.60)	13.10 (12.70, 13.50)	13.15 (12.80, 13.93)	0.020
RDW-SD,M(Q_1,Q_3)	43.50 (41.60, 45.65)	43.40 (41.50, 45.30)	43.95 (42.10, 46.60)	0.015
PLT, M (Q_1, Q_3)	214.00 (176.00,258.00)	218.00 (181.00,261.50)	207.50 (165.75,244.25)	0.027
NLR, M (Q_1, Q_3)	1.93 (1.47, 2.69)	1.86 (1.42, 2.49)	2.38 (1.73, 3.24)	<0.001
MLR, M (Q_1, Q_3)	0.21 (0.17, 0.28)	0.21 (0.16, 0.26)	0.25 (0.18, 0.33)	<0.001
PLR, M (Q_1, Q_3)	109.91 (85.63, 142.08)	109.38 (86.32, 140.56)	113.66 (83.96, 149.24)	0.420
SII, M (Q_1, Q_3)	420.95 (286.09,586.50)	411.01 (276.27,577.30)	463.19 (313.54,650.59)	0.049
SIRI, M (Q_1, Q_3)	0.80 (0.53, 1.22)	0.74 (0.50, 1.15)	0.99 (0.70, 1.44)	<0.001
SCI, M (Q_1, Q_3)	94.52 (72.78, 122.66)	94.89 (73.55, 122.27)	92.14 (71.20, 126.05)	0.920
PT, M (Q_1, Q_3)	11.80 (11.10, 12.80)	11.70 (11.00, 12.65)	12.15 (11.40, 13.20)	<0.001
INR, M (Q_1, Q_3)	0.98 (0.93, 1.02)	0.97 (0.93, 1.02)	1.00 (0.96, 1.06)	<0.001
APTT, M (Q_1,Q_3)	30.40 (26.35,34.70)	30.30 (26.25,34.55)	31.00 (26.50,35.32)	0.700
FIB, M (Q_1, Q_3)	2.84 (2.41, 3.35)	2.77 (2.35, 3.24)	3.15 (2.65, 3.91)	<0.001
TT, M (Q_1, Q_3)	16.60 (15.70,17.40)	16.60 (15.70,17.40)	16.45 (15.60,17.22)	0.248

Notes: Mean ± SD, means ± standard deviation; M(Q_1,Q_3), median (interquartile range); n(%), number (percentage).
Abbreviations: N, neutrophil count; L, lymphocyte count; M, monocyte count; E, eosinophil count; B, basophil count; HB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW-CV, red cell distribution width - coefficient of variation; RDW-SD, red cell distribution width - standard deviation; PLT, platelet count; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index; SCI, systemic coagulation and inflammation index; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; FIB, fibrinogen; TT, thrombin time.

Table 3 Blood Biochemical -Related Parameters of the Study Participants

Variables	Total (n = 511)	Non-PH (n = 403)	PH (n = 108)	P value
ALB, Mean ± SD	39.49 ± 3.65	39.79 ± 3.47	38.37 ± 4.10	0.001
TyG, M (Q_1, Q_3)	1.38 (1.05, 1.79)	1.43 (1.09, 1.82)	1.27 (0.95, 1.61)	0.012
GLB, M (Q_1, Q_3)	26.10 (23.70,28.50)	26.00 (23.50,28.40)	26.45 (24.30,29.20)	0.102
ALT, M (Q_1, Q_3)	21.00 (15.00, 30.50)	21.00 (16.00, 31.00)	19.00 (13.00, 28.25)	0.049
AST, M (Q_1, Q_3)	21.00 (17.00, 25.50)	21.00 (17.00, 25.00)	21.50 (17.00, 28.25)	0.353
LDH, M (Q_1, Q_3)	170.00 (150.50,198.00)	169.00 (149.00,195.00)	172.00 (155.00,209.00)	0.034
α-HBDH M (Q_1, Q_3)	113.00 (97.50, 129.00)	111.00 (97.00, 126.00)	121.50 (99.00, 139.00)	0.001
CK, M (Q_1, Q_3)	83.00 (59.00, 121.50)	85.00 (62.00, 120.00)	78.50 (51.50, 130.75)	0.113
CKMB,M(Q_1,Q_3)	11.00 (9.00, 14.00)	11.00 (9.00, 14.00)	11.00 (9.00, 14.25)	0.607
Ur, M (Q_1, Q_3)	4.90 (4.10, 5.91)	4.90 (4.13, 5.83)	4.90 (3.94, 6.23)	0.780
Cr, M (Q_1, Q_3)	73.00 (63.00, 85.50)	72.00 (63.00, 84.00)	75.00 (64.75, 90.25)	0.117
UA, M (Q_1, Q_3)	370.00 (308.50,440.00)	366.00 (305.50,432.50)	388.50 (321.75,469.00)	0.053
TC, M (Q_1, Q_3)	4.42 (3.67, 5.07)	4.47 (3.74, 5.10)	4.22 (3.40, 4.73)	0.003
TG, M (Q_1, Q_3)	1.55 (1.12, 2.17)	1.61 (1.17, 2.31)	1.33 (1.04, 1.76)	<0.001
HDL-C, M(Q_1,Q_3)	1.05 (0.91, 1.23)	1.04 (0.91, 1.23)	1.06 (0.93, 1.25)	0.596

(*Continued*)

Table 3 (Continued).

Variables	Total (n = 511)	Non-PH (n = 403)	PH (n = 108)	P value
LDL-C, M(Q_1,Q_3)	2.76 (2.19, 3.25)	2.78 (2.26, 3.29)	2.62 (1.89, 3.16)	0.012
Non-HDL-C,M(Q_1,Q_3)	3.32 (2.61, 3.92)	3.38 (2.76, 3.95)	3.04 (2.39, 3.76)	0.004
Lpa, M (Q_1, Q_3)	8.10 (5.20, 17.40)	8.10 (5.20, 17.10)	9.20 (4.97, 18.55)	0.620
ApoA1, M (Q_1,Q_3)	1.22 (1.11, 1.37)	1.23 (1.11, 1.35)	1.20 (1.09, 1.40)	0.407
ApoB, M (Q_1, Q_3)	0.87 (0.71, 1.03)	0.87 (0.73, 1.04)	0.80 (0.67, 1.02)	0.067
FPG, M (Q_1, Q_3)	5.10 (4.57, 5.84)	5.07 (4.56, 5.71)	5.38 (4.63, 6.24)	0.030

Notes: Mean ± SD, means ± standard deviation; M(Q_1,Q_3), median (interquartile range); n(%), number (percentage).
Abbreviations: ALB, albumin; TyG, triglyceride glucose index; GLB, globulin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; α-HBDH, alpha-hydroxybutyrate dehydrogenase; CK, creatine kinase; CK-MB, creatine kinase-MB isoenzyme; Ur, urea; Cr, creatinine; UA, uric acid; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; Lpa, lipoprotein(a); ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; FPG, fasting plasma glucose.

Table 4 PSG and TTE Parameters of the Study Participants

Variables	Total (n = 511)	Non-PH (n = 403)	PH (n = 108)	P value
AHI, M (Q_1, Q_3)	25.70 (16.85, 35.70)	24.60 (16.20, 32.85)	35.35 (21.15, 51.52)	<0.001
ODI, M (Q_1, Q_3)	22.90 (12.50, 36.15)	20.10 (11.35, 30.30)	37.45 (23.27, 55.23)	<0.001
$MSaO_2$, M (Q_1, Q_3)	90.50 (88.00, 92.00)	90.80 (88.95, 92.10)	88.00 (85.00, 90.75)	<0.001
$LSaO_2$, M (Q_1, Q_3)	77.00 (67.50, 81.00)	78.00 (72.00, 82.00)	69.50 (60.00, 77.00)	<0.001
CO, M (Q_1, Q_3)	5.20 (4.90, 5.70)	5.30 (4.90, 5.80)	5.20 (4.75, 5.70)	0.415
LVEF, M (Q_1, Q_3)	67.00 (63.00, 70.00)	67.00 (64.00, 70.00)	67.00 (62.00, 70.00)	0.108

Notes: Mean ± SD, means ± standard deviation; M(Q_1,Q_3), median (interquartile range); n(%), number (percentage).
Abbreviations: AHI, apnea-hypopnea index; ODI, oxygen desaturation index; $MSaO_2$, mean arterial oxygen saturation; $LSaO_2$, lowest arterial oxygen saturation; CO, cardiac output; LVEF, left ventricular ejection fraction.

Factor Selection for Nomogram Construction

The 511 OSA patients included in the study were randomized in a 7:3 ratio into a training set (n=357) and a validation set (n=154) for model development and validation, respectively.

Univariate Logistic Regression for Preliminary Screening of Potential Risk Factors

In the training set, we used the occurrence of PH in OSA patients as a binary outcome variable and applied univariate logistic regression analysis to preliminarily screen for potential risk factors associated with the development of PH. The results of the analysis showed that the risk factors including age, age subgroups (using 60 years as the boundary), BMI, recent pulmonary infection, hypertension, CHD, AHI, ODI, $MSaO_2$, $LSaO_2$, LVEF, N, MCHC, RDW-CV, RDW-SD, NLR, MLR, SII, SIRI, SCI, ALB, GLB, LDH, α- HBDH, TC, Non-HDL-C, FBG, PT and FIB, a total of 29 indices, were significantly associated with PH in OSA patients ($P < 0.05$; Figure 2).

Multiple Collinearity Test and Lasso Regression for Further Selection of Risk Factors

We first performed a multicollinearity test for the 29 potential risk factors and assessed the severity of collinearity by calculating the VIF. According to the standard,[27] a VIF value greater than 10 was considered to indicate severe collinearity, and such variables were excluded from subsequent analysis. The results showed that the variables with VIF values less than 10 included age, age subgroups (using 60 years as the boundary), BMI, recent pulmonary infection, hypertension, CHD, AHI, ODI, $MSaO_2$, $LSaO_2$, LVEF, N, MCHC, RDW-CV, RDW-SD, NLR, MLR, SII, SCI, ALB, GLB, LDH, α-HBDH, FBG, PT, and FIB, totaling 26 indicators. Subsequently, these variables were included in the Lasso regression for further feature selection. By linearly combining the factors weighted by the coefficients assigned to each subject and calculating the risk scores, we plotted the coefficient distribution curve of Lasso regression (Figure 3A). In addition, by using ten-fold cross-validation, we plotted the cross-validation mean squared error plot of Lasso regression ((Figure 3B). To prevent the model from overfitting and improve its

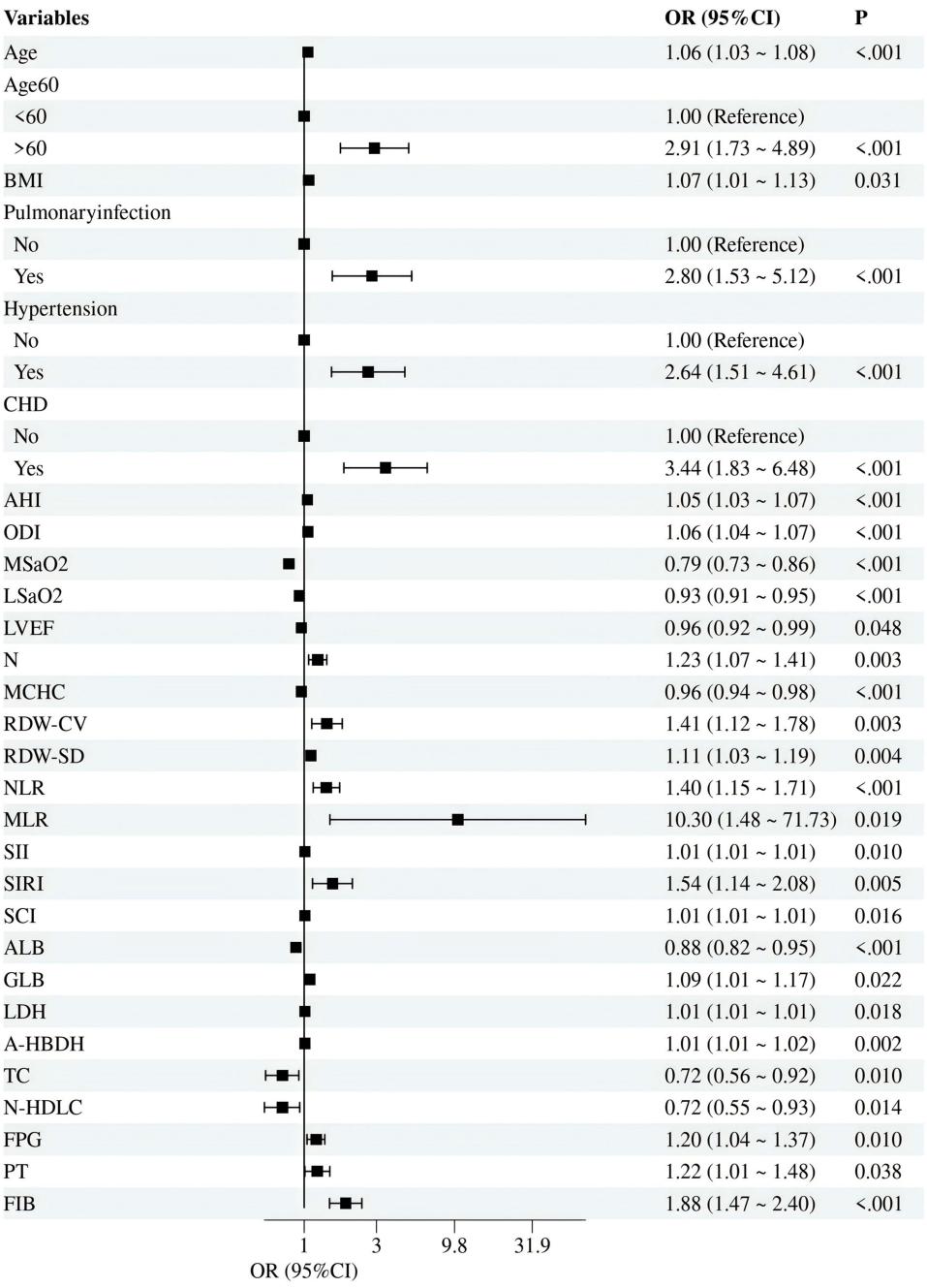

Figure 2 Univariate logistic regression forest plot.

Abbreviations: Age 60, age subgroups (using 60 years as the boundary); BMI, body mass index; CHD, coronary atherosclerotic heart disease; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; $MSaO_2$, mean arterial oxygen saturation; $LSaO_2$, lowest arterial oxygen saturation; LVEF, left ventricular ejection fraction; N, neutrophil count; MCHC, mean corpuscular hemoglobin concentration; RDW-CV, red cell distribution width - coefficient of variation; RDW-SD, red cell distribution width - standard deviation; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index; SCI, systemic coagulation and inflammation index; ALB, albumin; GLB, globulin; LDH, lactate dehydrogenase; A-HBDH, alpha-hydroxybutyrate dehydrogenase; TC, total cholesterol; N-HDLC, non-high-density lipoprotein cholesterol; FPG, fasting plasma glucose; PT, prothrombin time; FIB, fibrinogen.

generalization ability, ensuring good predictive performance on different data, we chose the λ value corresponding to the minimum mean squared error (λ-min) as the optimal penalty coefficient. Ultimately, we identified 10 non-zero predictive variables, including age, recent pulmonary infection, CHD, AHI, ODI, $MSaO_2$, $LSaO_2$, LVEF, α-HBDH, and FIB.

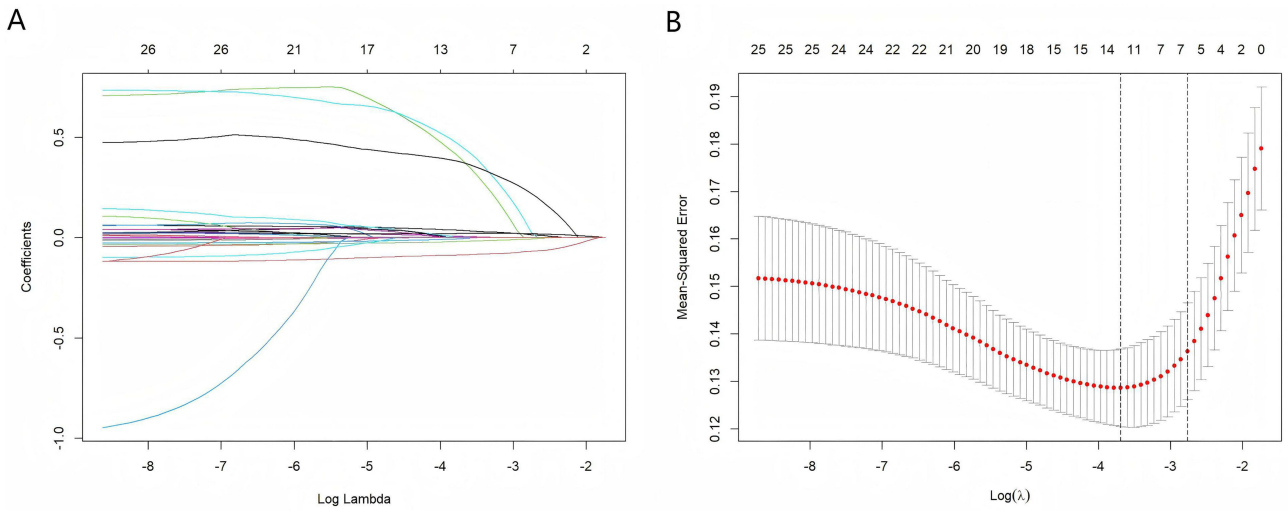

Figure 3 Lasso regression (**A**). Lasso regression coefficient distribution curve. (**B**). Cross-validation mean squared error plot of Lasso regression, with black vertical lines identifying the optimal predictive variables at the minimum λ-value (λ-min) and one standard error away from the λ-value (λ-se), respectively.

Multivariate Logistic Regression to Identify Independent Risk Factors and Construct a Nomogram Prediction Model

The 10 predictive variables (age, recent pulmonary infection, coronary heart disease, AHI, ODI, $MSaO_2$, $LSaO_2$, LVEF, α-HBDH, and FIB) selected by Lasso regression were further subjected to multivariate logistic regression analysis using the two-way stepwise regression to identify the final independent risk factors. The results of the multivariate logistic regression analysis showed that age, recent pulmonary infection, CHD, AHI, $MSaO_2$, $LSaO_2$, α-HBDH, and FIB, a total of 8 variables, are independent risk factors for the development of PH in patients with OSA (Table 5). Based on these 8 independent predictive factors, a nomogram prediction model for the occurrence of PH in OSA patients was constructed using the "rms" package in R software (Figure 4).

Validation of the Nomogram

In validating the effectiveness of the model, we performed a comprehensive assessment in three dimensions: discrimination, calibration, and clinical applicability. First, based on the training and validation sets, we plotted the ROC of the nomogram and calculated the AUC (Figure 5). The results showed that the AUC was 0.867 for the training set and 0.849 for the validation set, both of which were higher than 0.7, indicating that the model has good discrimination ability and high predictive accuracy. Second, we evaluated the fit of the model using the Hosmer-Lemeshow goodness-of-fit test. The *P*-values for both the training set

Table 5 Multivariate Logistic Regression Results for Predicting PH in Patients with OSA

Variables	β	S.E	Z	P	OR (95% CI)
Age	0.06	0.01	4.27	<0.001	1.06 (1.03 ~ 1.09)
Pulmonary infection	0.86	0.42	2.03	0.042	2.37 (1.03 ~ 5.44)
CHD	0.85	0.40	2.10	0.036	2.33 (1.06 ~ 5.13)
AHI	0.04	0.01	3.90	<0.001	1.04 (1.02 ~ 1.06)
$MSaO_2$	−0.12	0.05	−2.44	0.015	0.89 (0.81 ~ 0.98)
$LSaO_2$	−0.04	0.02	−1.90	0.058	0.96 (0.93 ~ 1.00)
α-HBDH	0.01	0.00	1.44	0.150	1.01 (1.00 ~ 1.02)
FIB	0.59	0.15	3.85	<0.001	1.81 (1.34 ~ 2.45)

Abbreviations: CHD, coronary atherosclerotic heart disease; AHI, apnea-hypopnea index; $MSaO_2$, mean arterial oxygen saturation; $LSaO_2$, lowest arterial oxygen saturation; α-HBDH, alpha-hydroxybutyrate dehydrogenase; FIB, fibrinogen.

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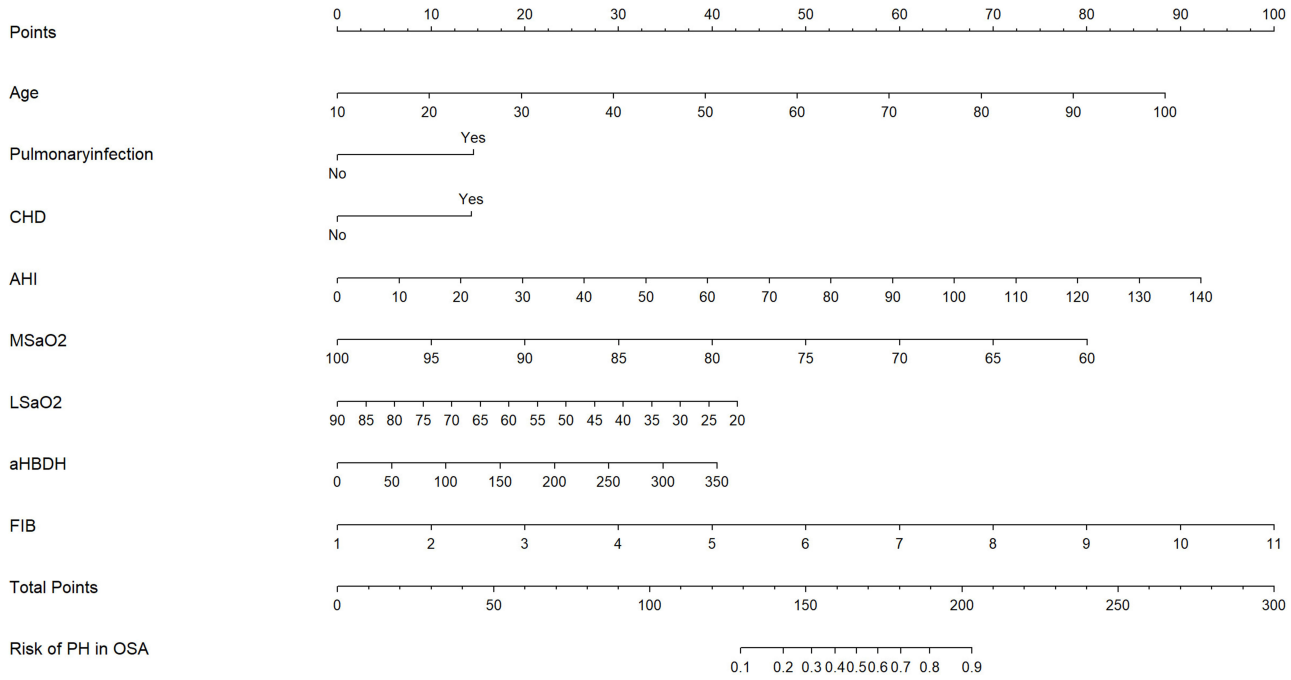

Figure 4 Nomogram for predicting the risk of OSA patients developing PH.
Abbreviations: CHD, coronary atherosclerotic heart disease; AHI, apnea-hypopnea index; $MSaO_2$, mean arterial oxygen saturation; $LSaO_2$, lowest arterial oxygen saturation; α-HBDH, alpha-hydroxybutyrate dehydrogenase; FIB, fibrinogen.

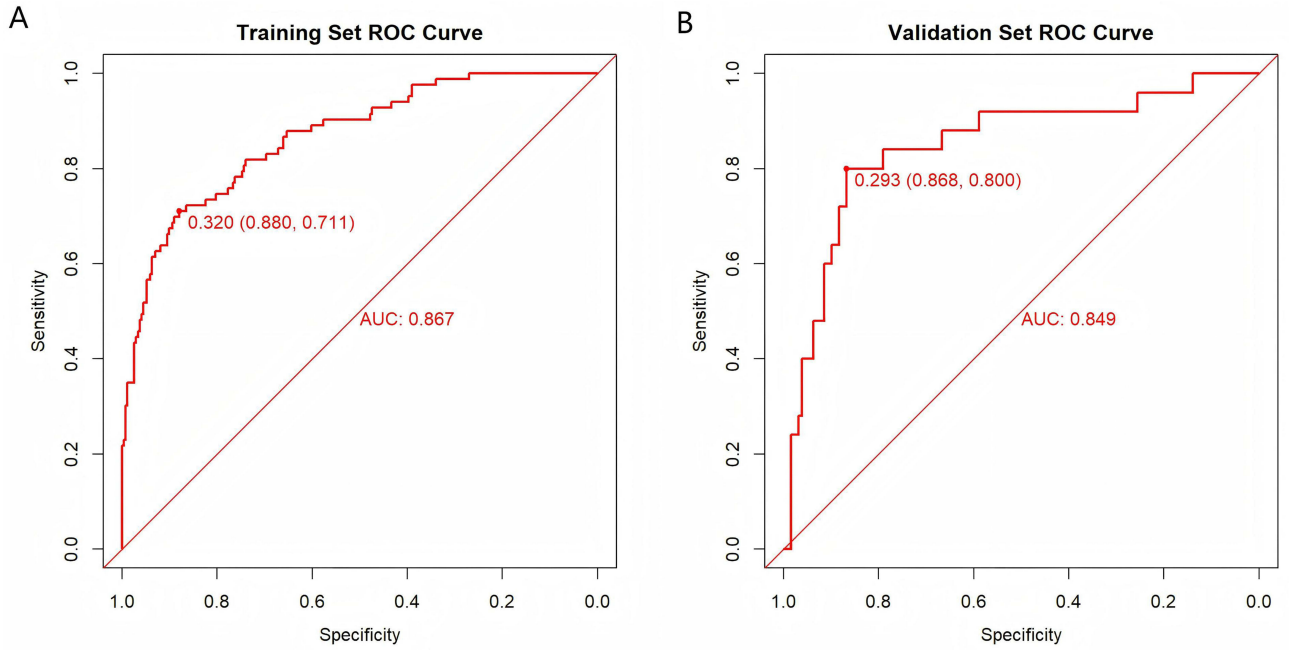

Figure 5 ROC curves of the model in the training set (**A**) and validation set (**B**).
Abbreviation: AUC, the area under the curve.

(P = 0.233) and the validation set (P = 0.283) were greater than 0.05, indicating that the model fits well. In addition, the calibration curves for both the training and validation sets demonstrated good consistency between the nomogram predictions and actual observations, indicating that the model has good calibration ability and high consistency (Figure 6). Finally, by plotting the DCA for the training and validation sets (Figure 7), we find that the nomogram has a superior overall net benefit over a wide range of

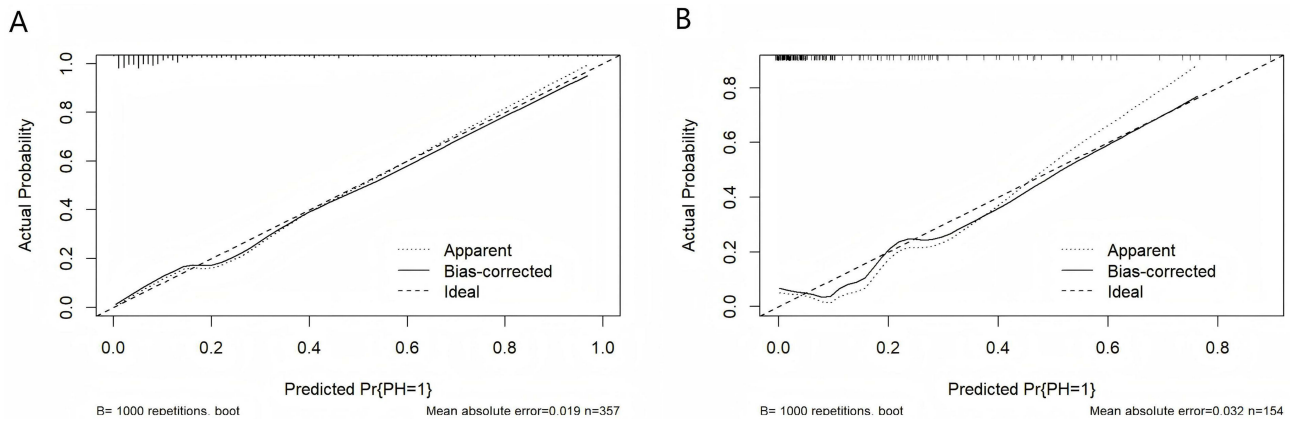

Figure 6 Calibration curves of the model in the training set (**A**) and validation set (**B**).

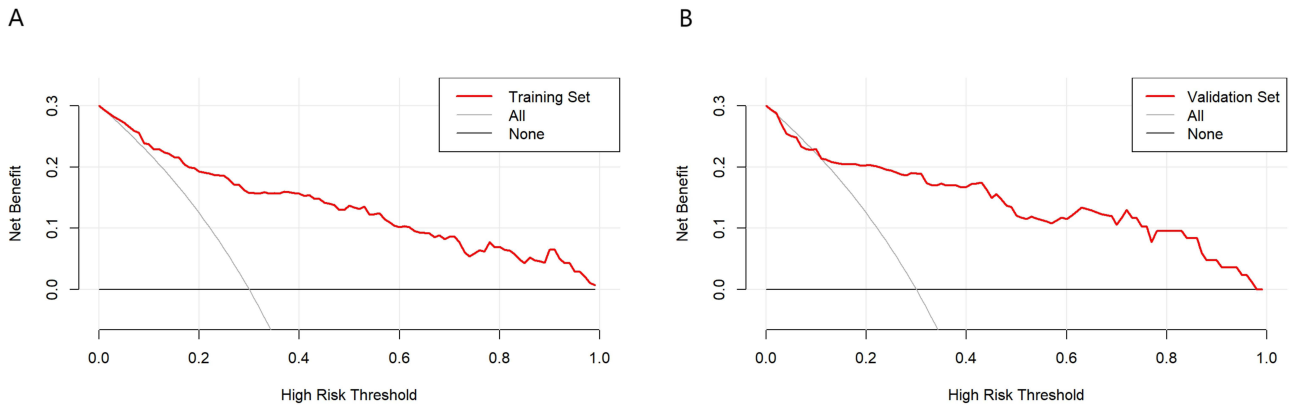

Figure 7 Decision curve analysis (DCA) of the model in the training set (**A**) and validation set (**B**).
Note: The x-axis (High-Risk Threshold) represents the risk threshold for the occurrence of PH in OSA patients, and the y-axis (Net Benefit) represents the net benefit for patients. The gray line (All) indicates that all patients were intervened, and the black line (None) indicates that all patients were not intervened. The red line indicates that the intervention was performed for each patient based on the model's prediction thresholds in the training and validation sets.

actual threshold probabilities, indicating that the model has good clinical applicability and practicality. In summary, the nomogram has good predictive ability and can effectively identify high-risk populations of PH among OSA patients.

Development of a Web-Based Nomogram

A web-based nomogram for predicting the risk of PH in OSA patients (https://osa-ph.shinyapps.io/dynnomapp/) was developed by using the "DynNom" package in R software and the web development platform: https://www.shinyapps.io/. By converting the nomogram into an online risk calculator, we further facilitated its clinical application (Figure 8).

Discussion

Available research evidence indicates a close relationship between OSA and PH, with a significantly increased prevalence of PH in OSA patients and vice versa,[2,13,14] suggesting that these diseases often coexist and may influence each other. IH is currently considered the core pathogenesis of PH in OSA,[29,30] triggering oxidative stress, inflammation, sympathetic activation, and hypercoagulability, all of which contribute to the development of PH.[31–35] In addition, sleep fragmentation caused by OSA can lead to autonomic dysfunction and activation of the renin-angiotensin-aldosterone system (RAAS) to promote PH.[21,36] These factors often act synergistically in PH progression. OSA is recognized as an independent risk factor for cardiopulmonary vascular diseases, significantly increasing morbidity and mortality rates, including in PH.[2] However, clinicians often overlook the impact of OSA on PH progression, leading to delayed diagnosis and potential irreversible right heart damage, severely affecting treatment outcomes. Therefore, early screening for PH in

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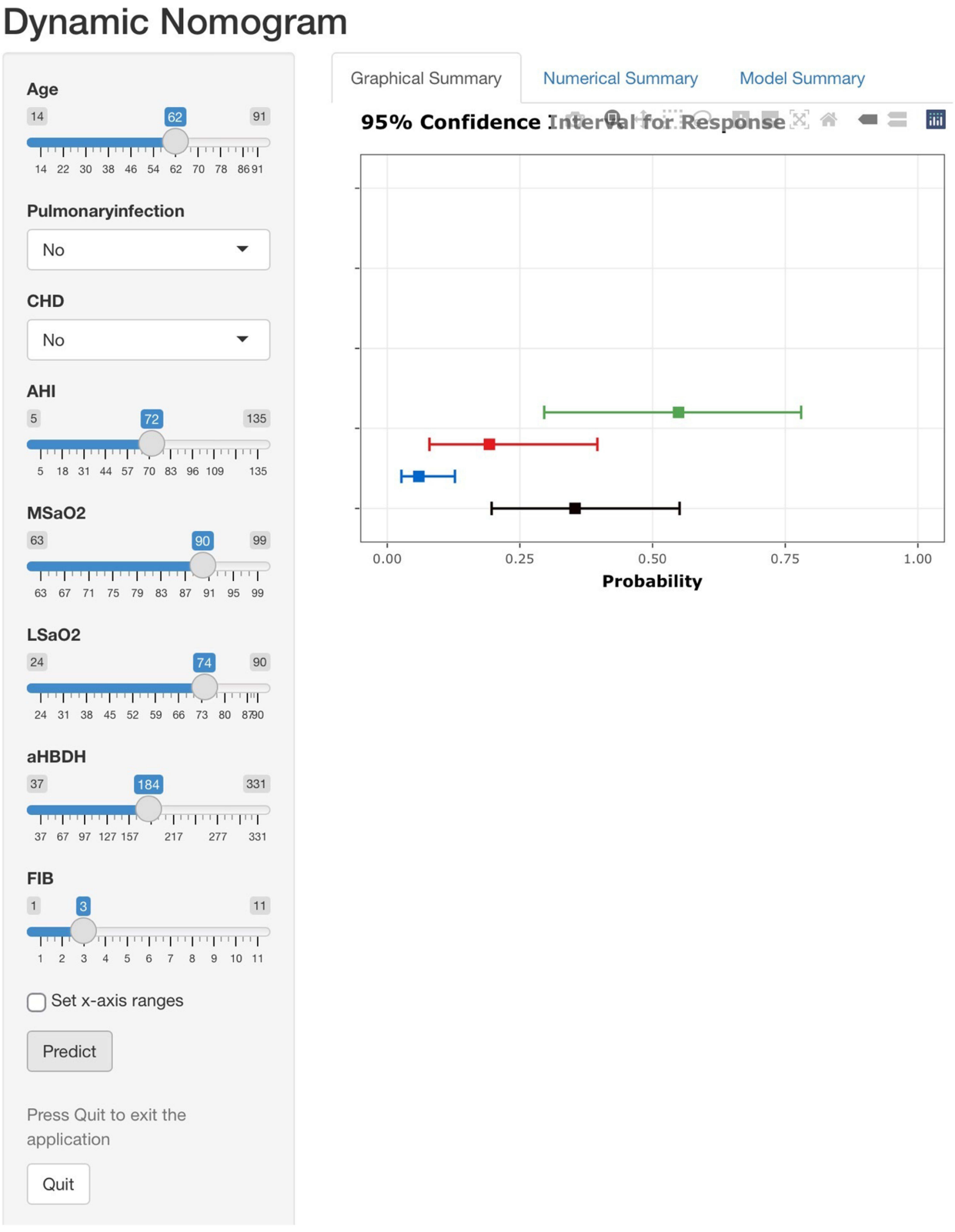

Figure 8 A web-based nomogram for predicting the risk of PH in OSA patients.
Note: Reproduced from Available from shinyapps.io by Posit; https://osa-ph.shinyapps.io/dynnomapp/[28].

OSA patients is crucial. Currently, TTE is the main method for PH diagnosis and screening, but variability among examiners and regional diagnostic criteria hinders uniformity. Therefore, developing a simple risk prediction model based on RHC and clinical indicators for early PH screening is necessary.

In this study, we developed and validated a web-based nomogram to predict PH risk in OSA patients. The nomogram included eight independent predictors: age, recent pulmonary infection, CHD, AHI, $MSaO_2$, $LSaO_2$, α-HBDH, and FIB. Except for MSaO2 and LSaO2, which are negatively correlated with PH occurrence, the other factors are positively correlated. To our knowledge, this is the first dynamic nomogram model for assessing the risk of developing PH in OSA patients. Our findings will help clinicians in identifying high-risk PH patients for early intervention, thereby delaying disease progression, reducing complications, and improving quality of life.

We identified age, recent pulmonary infection, and CHD as independent risk factors for PH in OSA patients. Among these factors, age is a recognized common risk factor for both OSA and PH, with prevalence increasing with age. Epidemiological data show OSA prevalence in adults ranges from 10% to 26%,[37] rising to 67.6% in those over 60.[38] Moreover, a large-scale observational study found that the risk of OSA increases 2.2-fold with every 10-year increase in age.[39] Studies of PH have also confirmed that the onset of PH is closely related to age and that older patients tend to have a poor prognosis.[8,9] A prospective study of 411 PH patients showed those over 65 years old had worse pulmonary diffusion function, more comorbidities, poorer treatment outcomes, and lower survival rates without transplantation.[40] Aging likely contributes to OSA through physiological changes such as decreased upper airway tension impaired respiratory function, and increased susceptibility to airway collapse.[41,42] OSA is often accompanied by other chronic diseases, such as hypertension, CHD, diabetes, chronic obstructive pulmonary disease (COPD), and interstitial lung disease, which may exacerbate the risk of PH as the age of OSA patients increases.[43–45] In addition, long-term adverse lifestyle factors, such as smoking and alcohol consumption, can also lead to pulmonary vascular damage and promote the occurrence and progression of PH.[46] Recent pulmonary infection is another independent risk factor for PH in OSA patients. Studies have demonstrated that OSA and pulmonary infections are closely related and that pulmonary infections may increase the risk of developing PH. Relevant studies link the severity of OSA to a higher risk of hospitalization for pneumonia, with severe OSA patients facing 1.87-fold the risk of non-OSA individuals.[47] Currently, there are few observational studies on the correlation between pulmonary infections and PH. Research on idiopathic pulmonary arterial hypertension (IPAH) patients reveals dysregulated inflammatory mediators in peripheral blood, with markers such as interleukin predicting PH prognosis,[48] suggesting a close relationship between infections, inflammation, and the development of PH. Recurrent sleep apnea in OSA patients may impair immune function and increase inflammatory responses, thereby increasing susceptibility to pulmonary infection.[47] These infections can activate inflammatory cells and release numerous inflammatory mediators, causing pulmonary vascular damage and inducing PH.[49] They can also impair respiratory function, exacerbate hypoxia, and further increase pulmonary arterial pressure.[9] CHD is a common metabolic cardiovascular disease that may contribute to the progression of OSA-related PH. Numerous studies have shown a close relationship between OSA and cardiovascular diseases such as CHD, identifying OSA as an independent risk factor.[50,51] OSA-related ventilatory treatments can alleviate OSA severity and reduce adverse cardiovascular effects.[52] However, research on the correlation between CHD and PH is limited. CHD may indirectly lead to PH by impairing left heart function.[53] Left heart disease, particularly PH associated with left heart failure (PH-LHF), is the most common cause of PH.[54] Related epidemiological studies have also supported this view.[55,56] Coronary artery disease (CAD) is considered to be a major risk factor and primary cause of heart failure.[57] Therefore, we hypothesize that CHD is an independent risk factor for PH. OSA primarily induces CHD through oxidative stress and systemic inflammation leading to atherosclerosis, and CHD can cause myocardial ischemia, hypoxia, or necrosis, resulting in left ventricular dysfunction and remodeling.[58] This leads to elevated left atrial and pulmonary venous pressures, indirectly increasing pulmonary arterial pressure and promoting PH progression.[53,59]

In addition, our study identified AHI, $MSaO_2$, and $LSaO_2$ from PSG parameters, and α-HBDH and FIB from serum indicators as important independent predictors of PH development in OSA patients. Numerous studies have demonstrated that AHI and nocturnal hypoxia are independent risk factors for the progression of PH, consistent with our findings. Lowery's prospective study[25] found that AHI and sleep-related hypoxia are risk factors for pulmonary arterial hypertension (PAH) and are closely associated with right ventricular dysfunction. Additionally, a retrospective analysis of 205

OSA patients who underwent RHC for pulmonary hemodynamic monitoring found that nocturnal hypoxemia is associated with elevated mean pulmonary arterial pressure, increased pulmonary vascular resistance, and right ventricular dysfunction, and chronic hypoxemia can impair pulmonary hemodynamics and promote the progression of PH.[60] AHI, $MSaO_2$, and $LSaO_2$, related to IH, which can assess OSA severity. IH is considered a key mechanism in the development of OSA-related PH. Therefore, clinicians should perform early PSG assessments in PH patients to monitor disease progression and initiate early treatment to reduce IH-induced vascular damage.α-HBDH is an important biochemical marker reflecting the activity of specific isoenzymes of lactate dehydrogenase (LDH), used for diagnosis and assessment of myocardial infarction and liver function impairment.[61] OSA may cause myocardial cell damage and subsequent cardiac dysfunction via IH, oxidative stress, and inflammation, potentially key in PH development caused by OSA.[62] As an important myocardial injury biomarker, α-HBDH might be an independent risk factor for PH in OSA patients. However, few studies currently explore the correlation between α-HBDH, OSA, and PH, and their direct association remains unconfirmed. The correlation and mechanism of action among them should be further explored through large-sample and prospective studies in the future. FIB is an important coagulation factor linked to various diseases, including cardiovascular diseases, malignancies, and diabetes.[63] Studies show a correlation between FIB and OSA. For instance, Shamsuzzaman[64] found that serum FIB levels in OSA patients positively correlate with AHI, indicating that OSA severity is independently associated with elevated serum FIB levels. Besides, a meta-analysis by Lin[65] showed that long-term CPAP therapy significantly reduces serum FIB levels in OSA patients. Though clinical studies on FIB and PH are limited, FIB is confirmed as an inflammation-related coagulation protein and an independent risk factor for various cardiovascular diseases.[66,67] Therefore, we speculate that FIB may be related to PH progression. It is currently believed that OSA triggers oxidative stress and systemic inflammatory responses through IH and sleep fragmentation, leading to elevated serum FIB levels, which in turn cause hypercoagulability and microthrombus formation, ultimately promoting the development of PH.[64,68]

In summary, despite the limited number of studies and clinical models currently available on the correlation between OSA and PH, the predictive variables included in our study are largely consistent with existing research findings, indicating that our model is rational and feasible. In the study, we performed multicollinearity tests on univariate logistic regression results, followed by Lasso regression for feature selection, and identified the final independent predictive factors using multivariate logistic regression. We then developed a web-based nomogram to predict PH risk in OSA patients. The model demonstrated excellent performance in discrimination, calibration, and clinical applicability. Moreover, the predictive variables are simple and readily available, and the web-based nomogram is easy to use, does not require complex calculations, and can be easily disseminated. Therefore, our web-based nomogram is an efficient clinical screening tool for early identification of high-risk PH populations among OSA patients, enabling timely intervention to prevent pulmonary hemodynamic deterioration and improve prognosis.

Limitation

This study has several limitations. First, as a single-center retrospective study, it relies on existing medical records, which limits the sample size and may introduce information and selection biases, and precludes further study of disease outcomes. Second, due to the infrequent use of RHC, we used TTE results as the diagnostic criterion for PH. This approach may compromise diagnostic accuracy due to potential insufficiencies in the experience and technical skills of echocardiography technicians, as well as the low sensitivity and specificity of TTE for mild PH, leading to potential underdiagnosis or misdiagnosis. Third, the nomogram model developed is based on OSA patient records from our institution and lacks external validation. Its performance in predicting PH among different populations in other regions remains unclear, and its generalizability is uncertain. Additionally, the model did not consider the impact of CPAP treatment. CPAP is a main treatment for OSA and may affect the development of PH. However, our study aimed to construct a model based on patients' initial clinical characteristics to predict PH before treatment. Future studies should incorporate CPAP use as a variable to further refine the predictive model. Fourth, we assumed RAP to be 10 mmHg when estimating PASP using TTE. This assumption is based on clinical guidelines (a typical RAP range of 5–15 mmHg), the special characteristics of OSA patients (higher RAP due to chronic hypoxia and intrathoracic pressure changes), and the need to simplify calculations with an acceptable error range. Although this assumption provides a reasonable estimate for most patients, other thresholds could be considered. Further

validation studies may be needed to confirm the optimal threshold for different patient populations. Finally, we excluded patients with COPD, pulmonary interstitial fibrosis, and other chronic pulmonary diseases to minimize confounding factors, which introduced selection bias. Future multicenter prospective studies should validate the nomogram in larger, diverse cohorts, including those undergoing RHC, to assess its sensitivity and specificity. Additionally, the impact of OSA coexisting with chronic pulmonary diseases on PH should be explored.

Conclusion

In this study, we identified eight independent risk factors for PH in OSA patients: age, recent pulmonary infection, coronary heart disease, AHI, $MSaO_2$, $LSaO_2$, α-HBDH, and FIB. Ultimately, we developed and validated a stable and efficient web-based nomogram to predict the probability of PH in OSA patients. This model offers a novel approach for the early identification of high-risk PH populations, assisting clinicians in making informed decisions and holding significant implications for delaying disease progression and improving patient prognosis.

Data Sharing Statement

The data utilized to support the findings of this study are available from the corresponding author and first author upon reasonable request.

Ethics Approval and Informed Consent

The authors bear full responsibility for the work, guaranteeing that any doubts about the precision or consistency of any portion are adequately scrutinized and resolved. This research was conducted in compliance with the 2013 revision of the Declaration of Helsinki. The study was approved by the Second Affiliated Hospital of Kunming Medical University research committee. Informed consent was obtained from all patients included in the study.

Acknowledgments

The authors thank the medical staff in the Department of Respiratory Medicine and Critical Care Medicine of the Second Affiliated Hospital of Kunming Medical University for their support and help.

Author Contributions

Rou Zhang: Conceptualization, Methodology, Investigation, Formal analysis, Writing-original draft. Zhijuan Liu: Data curation, Formal analysis, Validation, Writing-review & editing. Ran Li: Software, Visualization, Formal analysis, Validation, Writing-review & editing. Li Ai: Conceptualization, Methodology, Validation, Writing-review & editing. Yongxia Li: Conceptualization, Methodology, Formal analysis, Study design, Writing-review & editing. All authors have contributed to the research and manuscript preparation, and have given final approval of the version to be published. We agreed to submit the article to the current journal and undertake to be accountable for all aspects of the work.

Funding

The authors received no specific funding for this work.

Disclosure

The authors have no conflicts of interest to declare.

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