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ORIGINAL RESEARCH

Development and Validation of a Nomogram for Predicting Non-Adherence to Continuous Positive Airway Pressure Therapy in Patients with Obstructive Sleep Apnea

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Background: Continuous positive airway pressure (CPAP) is an effective treatment for obstructive sleep apnea (OSA), but its long-term efficacy is limited by poor patient adherence. This study aimed to develop and validate a predictive nomogram for CPAP non-adherence in patients with OSA.

Methods: This is a secondary analysis of a retrospective study. A cohort of 695 Danish patients with OSA were followed for 3 years after initiating CPAP therapy. Independently associated factors were evaluated using multivariate Cox regression, and then nomogram predicting adherence to CPAP use were constructed. The discrimination of the nomogram was assessed using receiver operating characteristic (ROC) curves, calibration curves and decision curve analysis (DCA).

Results: Pulmonary disease, oxygen desaturation index (ODI), Epworth Sleepiness Score (ESS) and severity of OSA were identified as predictors and incorporated into the nomogram. The nomogram demonstrated good discrimination with concordance index in training dataset (0.73, 95% CI: 0.69–0.78) and validation dataset (0.72, 95% CI: 0.66–0.79). ROC curve, calibration curve, and DCA indicated the nomogram had good clinical utility.

Conclusion: This study provided an effective nomogram for predicting CPAP non-adherence in OSA patients.

Keywords: continuous positive airway pressure, obstructive sleep apnea, nomogram, patient adherence, predictive model

Introduction

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder characterized by recurrent episodes of upper airway collapse during sleep, leading to complete or partial cessation of breathing ie hypoxaemia.[1] The characteristic symptoms of OSA include snoring, nocturnal breathing disturbances, and daytime somnolence. Long-term OSA has been associated with various adverse health outcomes, such as hypertension, cardiovascular disease, diabetes, and cognitive impairment, and may even contribute to sudden nocturnal death in severe cases.[2,3]

Continuous positive airway pressure (CPAP) therapy is the first-line treatment for OSA. CPAP utilizes a device to provide a constant flow of pressurized air through the nose or mouth, maintaining the patency of the upper airway and preventing apnea or hypoxemia.[4] However, despite the demonstrated efficacy of CPAP, many patients exhibit poor adherence to this treatment, which can compromise treatment outcomes and negatively impact the patient's quality of life.[5] Therefore, identifying the factors that influence CPAP adherence and implementing personalized interventions are crucial for improving CPAP adherence, enhancing the quality of life, and improving the long-term prognosis of patients with OSA. This study aims to develop and validate a predictive modeling framework to estimate the probability of non-adherence to CPAP use within 1–3

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years in patients with OSA. This model aspires to identify individuals at high risk of poor adherence before the initiation of treatment, enabling targeted interventions to maximize the likelihood of successful treatment.

Methods

Study Design

This was a secondary analysis of a large-scale retrospective observational study.[6] Data were obtained freely from the DATADRYAD database (available at www.datadryad.org). A total of 695 patients with OSA were consecutively collected at Silkeborg Hospital in Denmark from the 1st of January 2012 to the 28th of February 2013. The research mentioned that the Philips SystemOne REMstar autoCPAP and the ResMed S9 Autoset CPAP were used for patient treatment. Sleep disorder specialist nurses periodically adjust the CPAP settings, mask type, and humidification for all patients until they can tolerate the therapy well. Patients are required to undergo an annual follow-up evaluation at the clinic. The adherence to CPAP use is monitored through 3 years follow-up visits and the secure digital card data from the CPAP device. Patients are considered non-adherent if they decide to discontinue the treatment due to intolerance or perceived lack of benefit, or if they are lost to follow-up, defined as no response to any communication or requests for new masks, tubing, or filters. The previously published article have clearly stated that the study was approved by the Danish Health Authority and Danish Data Protection Agency in Central Region Denmark (Case number 1–16-02-30-13) with permission to store non-anonymized data in a secured research database.[6] The purpose of the previous study was to quantify the degree of non-adherence and describe its clinical characteristics, and its main conclusion was that the severity of OSA, subjective daytime sleepiness, and smoking status are independently related to adherence to CPAP therapy.[6] After re-analyzing the original data and performing multiple imputation to address the partial absence of data, we have made new discoveries. We can now expand on the previous research and develop a predictive model that can estimate the non-adherence rate to CPAP therapy for patients with OSA, and our study was approved by the Ethics Committee of the First People's Hospital of Changde City (2024–255-01).

Clinical Assessments

The following details were collected: gender, weight, body mass index (BMI), smoking, coexisting diseases (hypertension, diabetes, cerebrovascular disease, cardiovascular disease, pulmonary disease), sleeping condition (snoring, nycturia, hypnotic drugs, observed interrupted breathing), oxygen desaturation index (ODI), Epworth Sleepiness Score (ESS), severity of OSA, humidification and period with CPAP.

An apnea is defined as a cessation of airflow lasting ≥10 seconds, while a hypopnea is a reduction in airflow accompanied by a >3% drop in oxygen saturation.[7] The Apnea Hypopnea Index (AHI) represents the average number of apnea and hypopnea events per hour, used to categorize OSA severity: mild (AHI 5–15), moderate (AHI 15–30), and severe (AHI ≥30).[8] The Oxygen Desaturation Index (ODI) reflects the average number of ≥4% desaturation episodes per hour.[9]

Statistical Analysis

Normally distributed continuous data are expressed as mean ± standard deviation, and non-normally distributed continuous data are presented as median (Q1-Q3). Student's *t*-test or non-parametric tests are used for between-group comparisons. Categorical data are presented as numbers or percentages, and analyzed using Pearson's chi-square test or Wilcoxon rank-sum test for group comparisons. Due to the partial absence of original data, we added random forest interpolation and adopted R missForest package.[10] 70% of the patients are randomly allocated to the training set, and the remaining 30% are assigned to the validation set. In the training set, stepwise forward-backward Cox regression is performed, using Akaike Information Criterion (AIC) minimization as the variable selection criterion, to develop predictive models for 1-year and 3-year CPAP non-adherence in OSA patients. Nomograms are used to present the predictive models. The discriminative ability of the models is evaluated using the concordance index (C-index) in the training set. Calibration curves are used to assess model calibration, and decision curve analysis (DCA) is performed to evaluate the clinical usefulness of the models. Furthermore, to further examine the discriminative ability of the proposed nomograms, patients in the training set are divided into four groups based on the quartiles of the total nomogram scores,

and Kaplan-Meier survival curves are plotted for each group, with between-group comparisons performed using the Log rank test. All statistical analyses are performed using STATA 18 software, and a two-sided p-value <0.05 is considered statistically significant.

Results

Patients Baseline Clinical Characteristics

A total of 695 patients were enrolled in the retrospective observational study, including 177 women and 518 men. The patient characteristics were listed in Table 1. Age was entirely absent from the original dataset and consequently was not incorporated into our study. Except for pulmonary disease, there were no significant differences among the following variables between the training set and validation set.

Independent Predictors for CPAP Non-Adherence in OSA

Through multivariate cox regression analysis, with AIC minimization as the predictor screening rule, we found that pulmonary disease (HR, 1.938; 95% CI, 1.064–3.527; P=0.03), ODI (HR, 0.986; 95% CI, 0.971–1.002; P=0.094), ESS (HR, 0.918; 95% CI, 0.878–0.960; P=0.000), severe OSA (HR, 0.294; 95% CI, 0.147–0.588; P=0.001), and moderate OSA (HR, 0.642; 95% CI, 0.390–1.057; P=0.081) were independent predictors for CPAP non-adherence in OSA patients (Table 2).

Table 1 Characteristics of the Training Set and Validation Set

Variables	Training Set (n=486)	Validation Set (n=209)	P value
Sex, n (%)			0.14
Female	116 (23.87)	61 (29.19)	
Male	370 (76.13)	148 (70.81)	
Body weight (kg), mean ± SD	97.43 ± 22.15	94.68 ± 21.49	0.13
BMI (kg/m2), mean ± SD	31.14 ± 6.50	30.25 ± 5.85	0.087
BMI (kg/m2), n (%)			0.58
Normal	63 (12.96)	33 (15.79)	
Overweight	193 (39.71)	83 (39.71)	
Obesity	230 (47.33)	93 (44.50)	
Diabetes, n (%)			0.99
No	444 (91.36)	191 (91.39)	
Yes	42 (8.64)	18 (8.61)	
Hypertension, n (%)			0.96
No	294 (60.49)	126 (60.29)	
Yes	192 (39.51)	83 (39.71)	
Cerebrovascular disease, n (%)			0.18
No	464 (95.47)	204 (97.61)	
Yes	22 (4.53)	5 (2.39)	
Cardiovascular disease, n (%)			0.93
No	452 (93.00)	194 (92.82)	
Yes	34 (7.00)	15 (7.18)	
Pulmonary disease, n (%)			0.008
No	435 (89.51)	200 (95.69)	
Yes	51 (10.49)	9 (4.31)	
Hypnotic drugs, n (%)			0.65
No	449 (92.39)	191 (91.39)	
Yes	37 (7.61)	18 (8.61)	
Nycturia, n (%)			0.52
No	119 (24.49)	56 (26.79)	
Yes	367 (75.51)	153 (73.21)	

(*Continued*)

Table 1 (Continued).

Variables	Training Set (n=486)	Validation Set (n=209)	P value
Smoking, n (%)			0.76
No	362 (74.49)	158 (75.60)	
Yes	124 (25.51)	51 (24.40)	
Snoring, n (%)			0.91
No	83 (17.08)	35 (16.75)	
Yes	403 (82.92)	174 (83.25)	
Observed interrupted breathing, n (%)			0.83
No	154 (31.69)	68 (32.54)	
Yes	332 (68.31)	141 (67.46)	
ESS, mean ± SD	10.69 ± 4.91	10.27 ± 4.83	0.30
ODI (events/h), mean ± SD	28.92 ± 24.19	25.44 ± 22.95	0.078
AHI (events/h), mean ± SD	35.93 ± 20.70	33.99 ± 20.54	0.26
Severity of OSA, n (%)			0.28
MILD	74 (15.23)	33 (15.79)	
Moderate	154 (31.69)	78 (37.32)	
Severe	258 (53.09)	98 (46.89)	
Humidification, n (%)			0.91
No	417 (85.80)	180 (86.12)	
Yes	69 (14.20)	29 (13.88)	
Period with CPAP without humidification (weeks), mean ± SD	130.98 ± 52.22	126.61 ± 54.07	0.32
Non-adherence, n (%)			0.035
No	397 (81.69)	156 (74.64)	
Yes	89 (18.31)	53 (25.36)	
Period with CPAP(weeks), mean ± SD	126.31 ± 56.32	118.37 ± 60.99	0.097

Abbreviations: BMI, body mass index; ESS, Epworth Sleepiness Score; ODI, oxygen desaturation index; AHI, apnea hypopnea index; OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure.

Table 2 Independent Predictors for CPAP Non-Adherence in OSA

Variables	HR	HR 95% CI	Z value	P value
Pulmonary disease	1.901	1.046–3.458	2.16	0.035
ODI	0.986	0.971–1.002	−1.68	0.080
ESS	0.920	0.880–0.962	−3.75	0.000
Moderate OSA	0.646	0.392–1.062	−1.74	0.085
Severe OSA	0.312	0.157–0.617	−3.47	0.001

Abbreviations: ODI, oxygen desaturation index; ESS, Epworth Sleepiness Score; OSA, obstructive sleep apnea; HR, hazard ratio; CI, confidence interval.

Development of Nomogram

Multivariate cox regression analyses implied that pulmonary disease, ODI, ESS and severity of OSA was identified as predictors (Figure 1). To use the nomogram, an individual patient's value is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers is located on the Total Points axis, and the total points projected to the bottom scale indicate the one-year, two-year, and three-year CPAP non-adherence rates for OSA patients. For example, a patient with moderate OSA and pulmonary disease, with an ODI value of 20 and an ESS value of 2, their total score is 183 (22.5+20+82.5+58). In this case, their 3-year non-adherence rate to CPAP therapy is 40%. To make it more convenient for OSA patients to predict the non-adherence rate of CPAP therapy, we created an online dynamic nomogram tool (https://lihui.shinyapps.io/DynNomapp2/). In the online tool, anyone can calculate the non-adherence rate of CPAP therapy in OSA patients based on the specific values of each indicator.

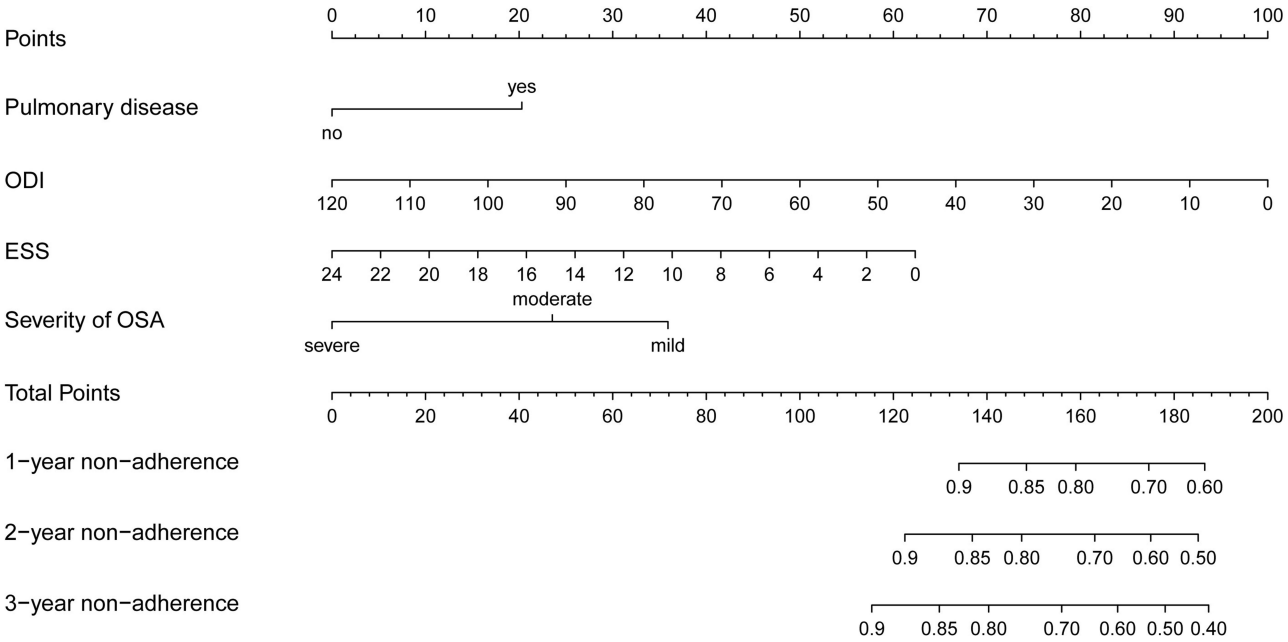

Figure 1 Nomogram predicting non-adherence of continuous positive airway pressure therapy in obstructive sleep apnea patients. To use the nomogram, it is first needed to determine the position of each variable on its axis and then plot a line with the specified value on the axis to determine the score of each variable. Next, the total score of all predictor variables is calculated below the nomogram to determine the probability of non-adherence.

Validation of the Nomogram

To determine the performance of the proposed nomogram in risk stratifying patients, we used Kaplan-Meier survival curve analysis to classify patients in the training and validation sets into four subgroups based on the quartiles of the total score of the nomogram. By performing time-dependent comparisons of subgroups with different levels of adherence, we found that the groups were well differentiated from each other, further validating the stability and accuracy of the nomogram in differentiating the level of patient non-adherence (Figure 2).

The bias-corrected C-indexes in the training set and validation set were 0.73 and 0.72 respectively (Table 2). For the one-year CPAP non-adherence rate, the area under the curve (AUC) of the ROC was 0.78 and 0.75 for the training and validation sets, respectively, and for the three-year CPAP non-adherence rate, the AUC of the ROC was 0.75 and 0.77 for the training and validation sets, respectively (Figure 3).

Calibration curves and DCA of the predictive models were plotted in the training and validation sets to visually assess the performance of the nomogram. The calibration curves for one-year and three-year predictions in the training dataset show better consistency between the predicted values and observed values, while the validation dataset showed slightly poorer consistency (Figure 4). The range of threshold probabilities for the DCA in both the training and validation sets showed better net clinical effects for the one-year and three-year prediction models, suggesting that the nomogram has certain clinical utility (Figure 5).

Discussion

CPAP treatment adherence refers to the duration of CPAP use per night and the proportion of nights CPAP was used during the observation period in OSA patients. Currently, the standard for good CPAP treatment adherence is considered to be that OSA patients use CPAP for more than 70% of the nights during the CPAP treatment observation period, with a usage time of at least 4 hours per night.[11] The longer the nightly CPAP usage time and the more days CPAP is used during the treatment period, the better the CPAP treatment adherence. Literature has shown that 8% to 15% of OSA patients refuse CPAP treatment on the first night, and at least 40% of patients stop using CPAP within the first year of treatment, with less than 50% of patients persisting with long-term treatment.[12,13] These studies indicate that improving CPAP treatment adherence is an important issue in OSA management.

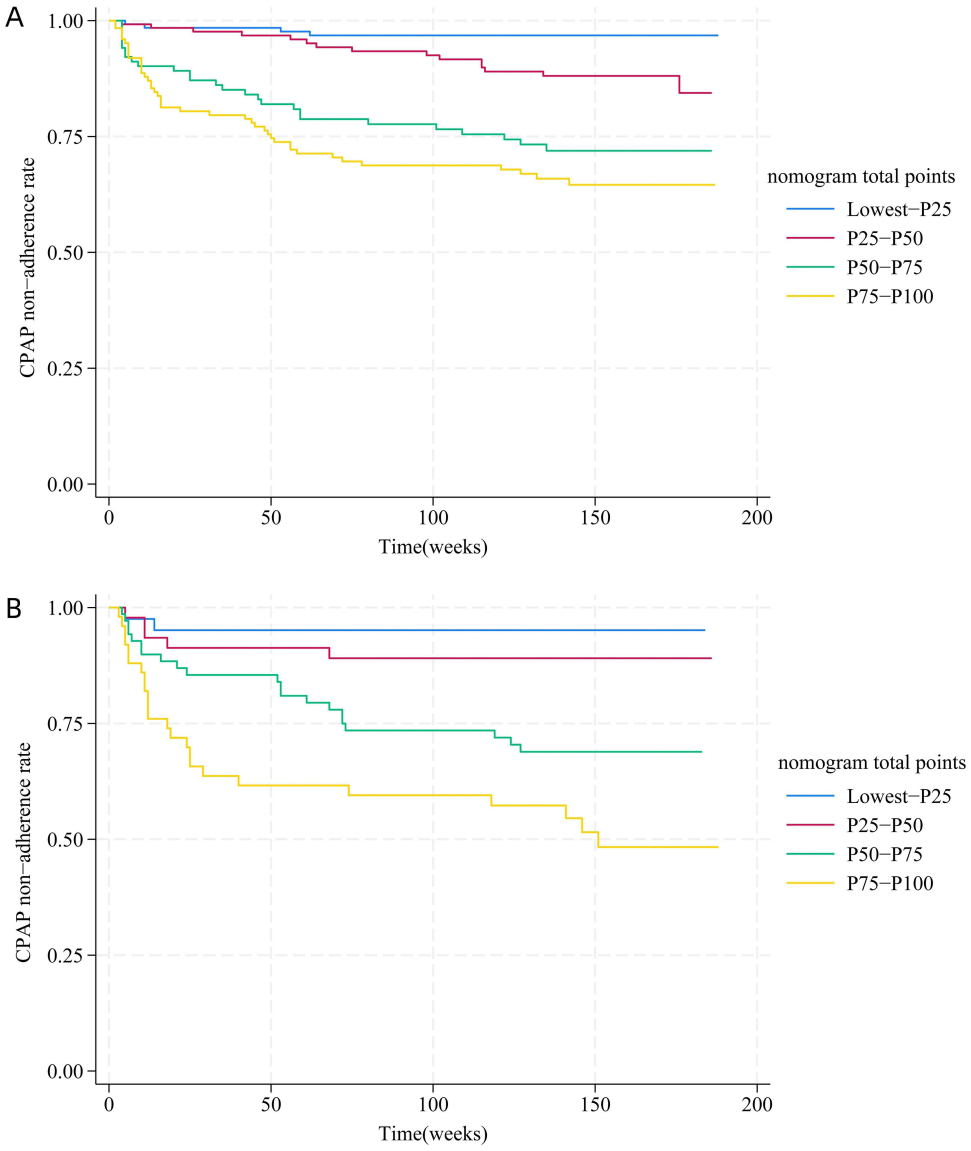

Figure 2 (**A**) Kaplan-Meier survival curves of training set categorized by the quartiles of proposed nomogram total points. (**B**) Kaplan-Meier survival curves of validation set categorized by the quartiles of proposed nomogram total points.

There is currently no simple and effective tool to predict CPAP treatment adherence in the clinical setting, which poses a challenge for clinicians' decision-making. This study successfully constructed and validated a nomogram to predict CPAP adherence in OSA patients, which can help clinicians identify high-risk patients for poor CPAP adherence early in the treatment and implement individualized intervention measures, such as enhanced health education and close follow-up, to improve CPAP adherence and treatment efficacy.

The nomogram integrates multiple key clinical factors, including pulmonary disease, ODI, ESS and the severity of OSA. For OSA patients with pulmonary diseases, especially those with comorbid chronic obstructive pulmonary disease (COPD) or other forms of lung function impairment, CPAP treatment may pose additional challenges. COPD patients may already have airway inflammation and airflow limitation, which can affect their acceptance and adherence to CPAP therapy.[14] Furthermore, the decline in lung function and pulmonary hypertension in COPD patients may increase the discomfort associated with CPAP therapy, such as nasal congestion, facial pressure, and dry cough.[15] The presence of pulmonary disease may also affect the efficacy of CPAP treatment. Even after CPAP treatment, COPD patients still face a higher risk of hospitalization and cardiovascular events,[16] indicating that the presence of pulmonary disease may limit

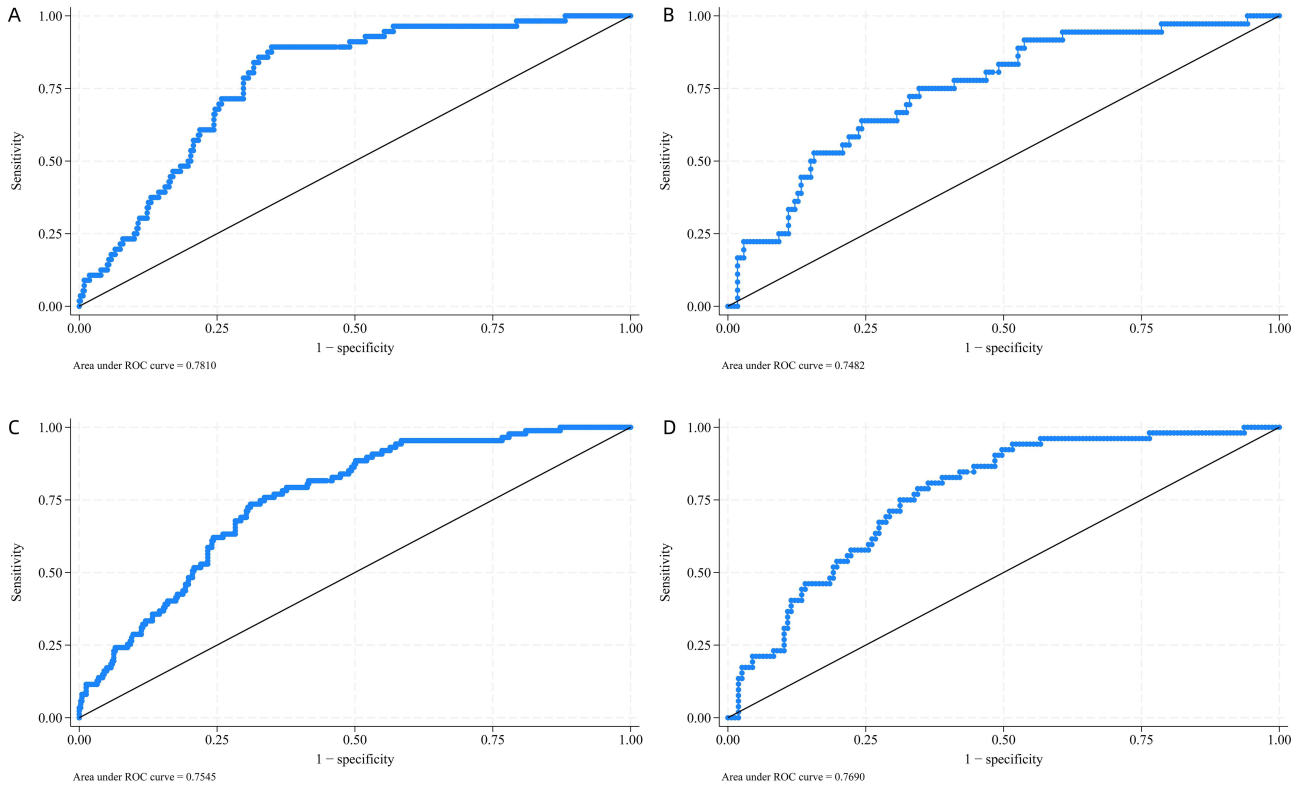

Figure 3 ROC analyses of nomogram for one-year and three-year CPAP non-adherence in OSA patients. (**A**) one-year in the training sets. (**B**) one-year in the validation sets. (**C**) three-year in the training sets. (**D**) three-year in the validation sets.

the treatment effect and influence long-term adherence. The pulmonary diseases identified in this nomogram as predictive factors are consistent with previous studies, indicating that comorbidities have a significant impact on CPAP adherence. However, in a systematic review it was mentioned that CPAP therapy can effectively improve the prognosis of patients with COPD-OSA overlap syndrome.[17] Therefore, compliance with CPAP therapy in this group of patients is of utmost importance. In addition, this emphasizes the critical role of comprehensive health assessment in formulating optimal treatment plans for these individuals.

ODI and ESS are two important indicators for evaluating CPAP adherence in OSA patients. These two indicators can reflect the patient's sleep quality and daytime sleepiness, indirectly affecting their acceptance and continued use of CPAP treatment.[18,19] The inclusion of ODI and ESS further highlights the role of objective sleep parameters and subjective symptoms in predicting adherence, revealing the complex nature of adherence behavior.

The adherence to CPAP treatment in mild, moderate, and severe OSA patients is influenced by multiple factors. Studies have shown that even mild OSA patients can experience significant improvements in quality of life after CPAP treatment, which may increase their adherence.[20] However, mild OSA patients' symptoms may be less obvious, leading to a lower perceived need for treatment, which can affect their adherence. Moderate and severe OSA patients' CPAP adherence may be influenced by more factors. On the one hand, these patients may be more likely to accept and persistently use CPAP due to more severe symptoms.[21] On the other hand, they may face a higher risk of non-adherence due to device discomfort, treatment side effects, or other personal issues. The research found that there are more upper airway obstruction problems in non-compliant CPAP users, which may be the main reason for the subjective discomfort and reduced CPAP adherence.[22] Furthermore, severe OSA patients may hesitate to undergo treatment due to concerns about potential side effects (such as gastroesophageal reflux).[23] Patients' psychological state, such as their expectations and coping strategies for the treatment, may also impact their adherence.[24]

The nomogram demonstrated good predictive performance in both the training set (concordance index of 0.73) and the validation set (concordance index of 0.72), as well as good clinical utility based on ROC curve, calibration curve and

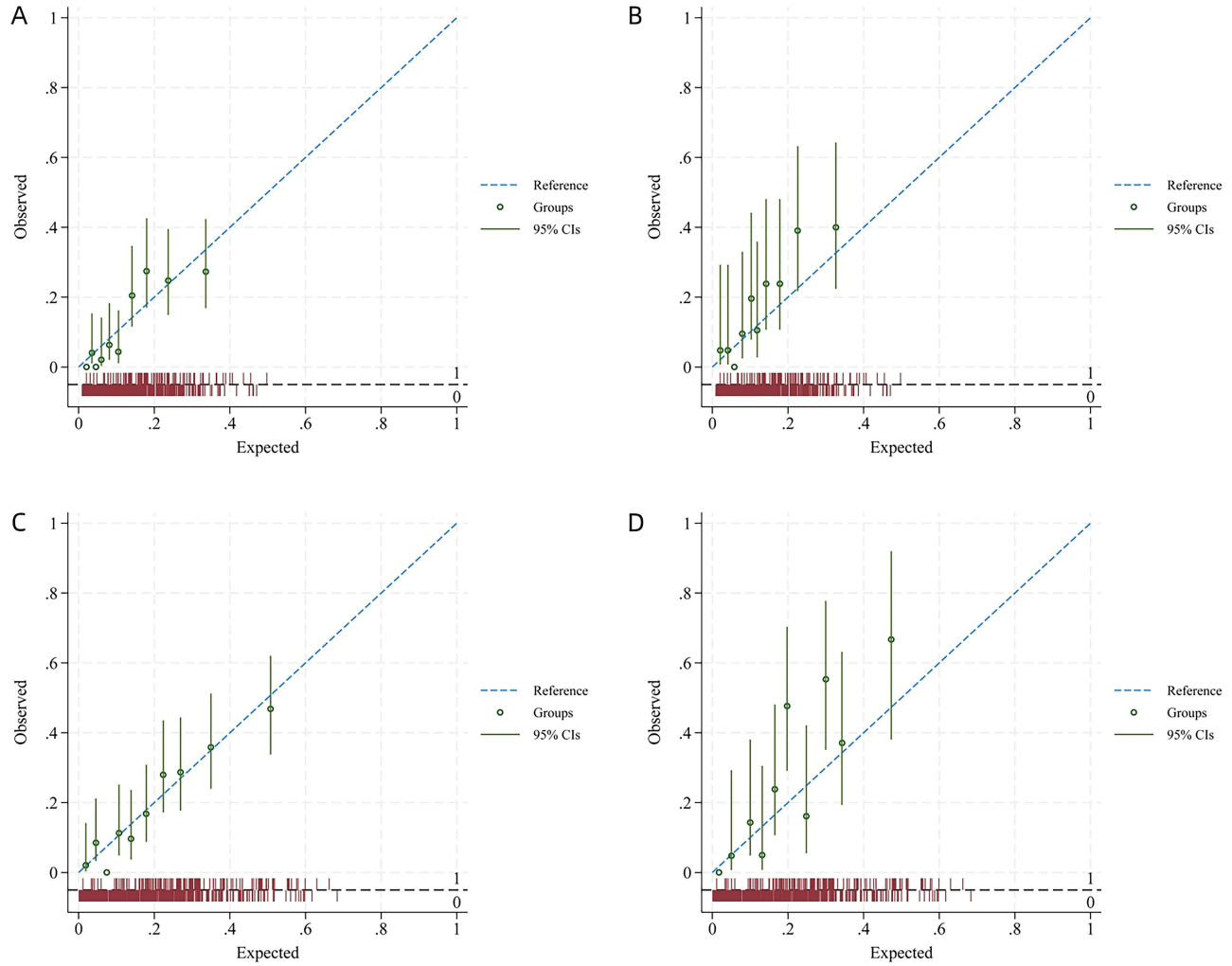

Figure 4 The calibration curves of the nomogram for one-year and three-year CPAP non-adherence in OSA patients. (**A**) one-year in the training sets. (**B**) one-year in the validation sets. (**C**) three-year in the training sets. (**D**) three-year in the validation sets.

DCA. Importantly, the nomogram maintained high predictive accuracy in the external validation cohort, enhancing confidence in its applicability to a broader population.

However, the study has some limitations. First, the use of humidification and nasal/oronasal masks,[25,26] which are important indicators of CPAP adherence, were not included in the baseline assessment due to inconsistent data. Second, as a retrospective analysis, there were inherent limitations, such as missing data points and the lack of BiPAP therapy utilization in the CPAP treatment. The lack of age, a key demographic variable, in our study may limit the generalizability of the research findings. If the age distribution of the OSA cohort is systematically skewed towards middle-aged and elderly individuals, not fully representing the entire OSA patient population, the model's predictive performance may deteriorate when applied to younger age groups. The absence of age information in the model may preclude it from adequately capturing the influence of age on CPAP adherence, potentially compromising the applicability of the predictive factors to other patient demographics. In clinical practice, physicians may need to consider patient age characteristics to deliver personalized adherence management strategies. However, the omission of age from the current predictive model may constrain its practical utility in guiding clinical decision-making. Furthermore, the study population was relatively homogeneous. Differences in cultural background, socioeconomic status, and healthcare systems may influence CPAP adherence patterns,[27] so future cross-regional validation studies would help improve the global applicability of the predictive nomogram developed. Additionally, the study only investigated CPAP adherence in OSA patients

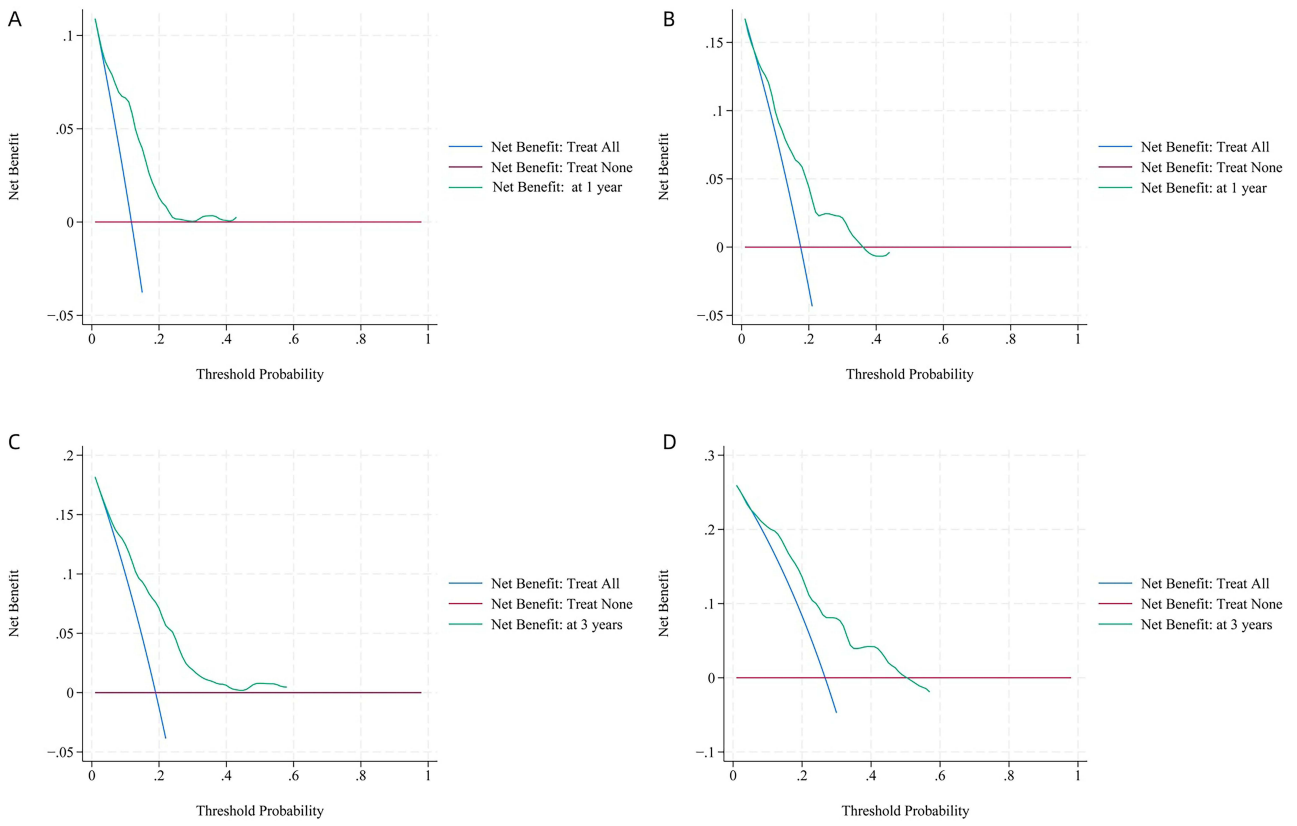

Figure 5 The decision curve analysis of the nomogram for one-year and three-year CPAP non-adherence in OSA patients. (**A**) one-year in the training sets. (**B**) one-year in the validation sets. (**C**) three-year in the training sets. (**D**) three-year in the validation sets.

for 1–3 years, and longer-term follow-up and the inclusion of more influencing factors may further improve the accuracy of the prediction model.

Conclusions

In conclusion, pulmonary disease, ODI, ESS and severity of OSA were demonstrated to be robust predictors of adherence to CPAP therapy in patients with OSA. The CPAP non-adherence prediction nomogram proposed in this study provides a valuable clinical decision-support tool for OSA treatment, facilitating the development of early intervention strategies and shared decision-making between clinicians and patients. By implementing personalized support measures for high-risk patients, the treatment efficacy and patient quality of life can be improved.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; have drafted or written, or substantially revised or critically reviewed the article; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Research by the authors was conducted without any commercial or financial relationships that may be construed as conflicts of interest.

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