

Development and Assessment of a Predictive Model for Obstructive Sleep Apnea in Chinese Adults: a Cross-sectional Population-based Study

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Research

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Abstract

Background:

Obstructive sleep apnea (OSA) is a kind of sleep respiratory disease with high prevalence and low diagnosis rate. With the progression of the disease, it will cause multiple organ damage, reduce the quality of life of patients and increase the economic burden. The aim of this study was to develop a predictive model of Chinese population suffering from OSA.

Methods:

We studied 120 patients who have visited our hospital from August 2018 to December 2020. Physical examination, demographic data, laboratory and ultrasound results and previous medical histories were collected. The least absolute shrinkage and selection operator method was used to select the risk factors of OSA and develop a predictive model. The accuracy of the predictive model was evaluated by C-index, calibration plot and receiver operating characteristic curve. The clinical application value of the predictive model was analyzed by decision curve analysis.

Results:

The predictive model contains 8 risk factors, including gender, body mass index, hypertension, diabetes mellitus, creatinine, blood urea nitrogen, serum uric acid and triglyceride. C-index of this predictive model is 0.898, and the area under curve of ROC curve is 0.894. Decision curve analysis showed that the predictive model was clinically useful.

Conclusion:

This predictive model could be conveniently used to predict the risk of OSA in the Chinese population.

Introduction

Obstructive sleep apnea (OSA) is a form of sleep-related breathing disorder in which patients experienced repeated reductions in airflow while asleep as a consequence of partial or total upper airway collapse [1]. Symptoms of OSA include fragmented sleep, recurrent apnea, intermittent snoring, and arousal, leading to daytime sleepiness and poor quality of sleep [2]. OSA patients experience a higher risk of stroke and chronic diseases including hypertension, arrhythmia, and coronary heart disease [3]. As symptoms typically occur during sleep and patients are unaware that they can be treated, OSA diagnosis is often delayed, further complicating efforts to treat this condition and imposing a more substantial medical and economic burden on affected individuals and families [4]. OSA diagnosis at an earlier time point can significantly decrease complication rates and associated medical costs [5], underscoring the need to recognize this condition as quickly as possible. Timely diagnosis and treatment are thus both crucial for high-risk OSA patients.

Rates of OSA among adults reported range from 6–17% [6], although this may be an underestimate given that diagnostic approaches are limited and many individuals may be unaware of the disease or its symptoms [7]. Polysomnography (PSG) is the gold standard approach to OSA patient diagnosis [1, 8], and is essential as a tool for assessing the severity of this condition based upon the apnea-hypopnea index (AHI). PSG, however, is a time- and resource-intensive diagnostic strategy that requires access to expensive equipment and highly-trained personnel, limiting its value as a routine screening tool for the diagnosis of OSA. There is thus a clear need for the development of a tool that can be routinely used to screen for OSA patients. OSA risk factors reportedly include age, sex, alcohol intake, smoking, upper airway anatomical abnormalities, and related diseases such as hypothyroidism [2]. However, there have been few reports regarding OSA-related independent risk factors following the exclusion of multicollinearity or corresponding predictive models.

The present study sought to design a model capable of effectively predicting OSA risk based upon available demographic data, laboratory information, examination results, and medical records.

Methods

Patients

In total, 120 patients that had visited the Ningbo Yinzhou No 2. Hospital between August 2018 and December 2020 were included in this study. Patients were excluded from this study if they were < 18 years of age or presented with severe cardiovascular or cerebrovascular disease. Demographic data and other questionnaire responses were collected by trained investigators in face-to-face interviews. Laboratory indices over a 3-month period, associated diseases, and abdominal ultrasound results were obtained from patient medical records. All patients had undergone PSG testing. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Ningbo Yinzhou No.2 Hospital. Patients provided written informed consent prior to study participation.

Data collection

Investigators obtained information pertaining to patient age, gender, alcohol intake, and smoking history through face-to-face interviews. Patient histories of hypertension (HTN) and diabetes mellitus (DM) were established through questionnaires and medical records. Venous blood samples were obtained from subjects in the morning following an 8 h fast, and were used to assess routine biochemical parameters such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyltransferase (γ -GGT), creatinine (Cr), blood urea nitrogen (BUN), serum uric acid (SUA), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein (LDL-C), and triglyceride (TG) were analyzed. Laboratory analyzer data were successfully standardized. Patient weight, height, and blood pressure were measured at the time of analysis following the removal of shoes, coats, and hats. Blood pressure was measured while patients had been seated at rest for at least 5 minutes. An ApneaLink Air (ResMed, Australia) was used for all PSG analyses, with OSA being diagnosed based upon an AHI \geq 5 times/h [2]

Definitions

1. HTN was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg in accordance with the criteria of the world health organization (WHO)[9].
2. DM was defined as fasting plasma glucose ≥ 7.0 mmol/h(126mg/L) or 2-h post glucose load plasma glucose ≥ 11.1 mmol/h(200mg/L) or both[10].
3. Overweight was defined as body mass index (BMI) ≥ 25 kg/m², Obesity was defined as BMI ≥ 30 kg/m² based on the WHO criteria[11].

Statistical analysis

Data were analyzed using R software (v 3.5.1). Optimal predictive features associated with OSA incidence were selected via the least absolute shrinkage and selection operator (LASSO) approach, which is well-suited to analyzing high-dimensional, low-sample size data with potential collinearity. Features were selected if they exhibited non-zero coefficients, and were used to construct a nomogram capable of predicting OSA risk.

Predictive nomogram accuracy was validated by plotting calibration curves that provided a graphical representation of the association between predicted and observed odds of OSA incidence. In total, 1000 bootstrap replications were used for this validation analysis. The probability of concordance between predicted and actual outcomes was assessed based upon Harrell's C-index, and the ability of the model to predict OSA incidence was assessed based upon area under the curve (AUC) values.

The clinical utility of the prepared nomogram was assessed via a decision curve analysis that quantified the net benefit at different threshold probability levels within this patient cohort. Net benefit was established by subtracting the proportion of false-positive patients from the true positive patients, and by comparing the potential harm associated with unnecessary intervention to the harm associated with failing to undergo treatment. $P < 0.05$ was the threshold of significance.

Results

Patient characteristics

Table 1 summarizes data pertaining to 18 different clinical and demographic variables analyzed for the 120 patients included in the present study. Variables including gender, smoking, drinking, HTN, DM, and fatty liver status are presented as dichotomous variables, whereas age, BMI, AST, ALT, γ GGT, Cr, BUN, SUA, TC, HDL, LDL, and TG are presented in the form of hierarchical enumeration data. Males made up the majority of patients in this study. Overall, patients were primarily between the ages of 40 and 60, with 63.3% being overweight or obese, and with 35%, 30.8%, and 36.7% of patients presenting with HTN, DM, and fatty liver, respectively.

Table 1
Baseline characteristics of all patient samples

Demographic characteristics	Total (n = 120)	
	No.	%
Gender		
Female	27	22.5
Male	93	77.5
Age (years)		
< 40	30	25.0
40–60	66	55.0
≥ 60	24	20.0
BMI (kg/m ²)		
< 25	44	36.7
25–30	50	41.7
≥ 30	26	21.6
Smoking		
No	90	75.0
Yes	30	25.0
Drinking		
No	98	81.7
Yes	22	18.3
Hypertension		
No	78	65.0
Yes	42	35.0
Diabetes Mellitus		
No	83	69.2
Yes	37	30.8
AST (U/L)		
< 40	112	93.3

Demographic characteristics	Total (n = 120)	
	No.	%
≥ 40	8	6.7
ALT (U/L)		
< 50	97	80.8
≥ 50	23	19.2
γGGT (U/L)		
< 60	98	81.7
≥ 60	22	18.3
Cr (μmol/L)		
< 104	116	96.7
≥ 104	4	3.3
BUN (mmol/L)		
< 7.14	115	95.8
≥ 7.14	5	4.2
SUA (μmol/L)		
< 416	84	70.0
≥ 416	36	30.0
TC (mmol/L)		
< 5.17	98	81.7
≥ 5.17	22	18.3
HDL (mmol/L)		
< 0.80	97	80.8
≥ 0.80	23	19.2
LDL (mmol/L)		
< 3.10	91	75.8
≥ 3.10	29	24.2
TG (mmol/L)		
< 2.26	79	65.8

Demographic characteristics	Total (n = 120)	
	No.	%
≥ 2.26	41	34.2
Fatty liver		
No	76	63.3
Yes	44	36.7

Feature selection and predictive model development

Risk scores were calculated based upon the linear combination of factors weighted by their corresponding coefficients, with a coefficient profile plot thereby being constructed. A cross-validated error plot for this LASSO regression model is shown in Fig. 1. Overall, this LASSO analysis reduced the 18 analyzed variables to 8 OSA-related predictors with nonzero coefficient values, including gender, BMI, HTN, DM, Cr, BUN, SUA, and TG. An easy-to-use predictive model incorporating these 8 independent factors was then established (Fig. 2).

OSA predictive model validation

Model validation was conducted via an intra-cohort analysis approach with 1,000 bootstrap replicates. This revealed that the model was in agreement with the correction curve, with an initial C-index value of 0.898 (95% CI: 0.833–0.963) that was confirmed to be 0.847 through bootstrap analyses (FigureS1). Given that this value was greater than 0.7, the model was considered satisfactory as a tool for predicting OSA incidence. A receiver operating characteristic (ROC) curve was further established to evaluate the utility of this model (FigureS2), with this curve exhibiting an AUC value of 0.894. These high C-index and AUC values indicated that this model was an effective predictive tool for gauging OSA risk.

Clinical use

The decision curve analysis of the OSA predictive model is presented in FigureS3. The decision curve showed that if the threshold probability of a patient and a doctor is > 28 and < 96%, using this OSA predictive model to intervene adds more benefit than the intervention-all-patients scheme or the intervention-none scheme.

Discussion

In an effort to predict OSA risk among Chinese adults, we herein developed a predictive model based upon eight objectives, easily measured variables associated with OSA incidence (Gender, BMI, HTN, DM, Cr, BUN, SUA and TG). In total, 120 patients were evaluated to develop this model, with 18 variables including demographic data, laboratory findings, ultrasound results, and comorbidities being assessed

via a LASSO approach to screen for significant risk factors linked to OSA incidence. The resultant predictive model exhibited good discrimination upon intra-cohort validation, with high C-index and AUC values suggesting that this model can be widely applied to screen for OSA risk.

Sex, age, obesity, snoring, pharyngeal abnormalities, and cephalometric features have all been identified as OSA-related risk factors in the general population [12, 13]. OSA rates are higher among males in regional surveillance studies [14], consistent with the identification of male sex as an independent predictor of OSA risk [15–17]. This may be linked to the fact that males are more likely to exhibit central weight gain than are females, leading to more upper airway fat storage [18]. Hormones may also influence OSA pathogenesis, as evidenced by the fact that it is more common among post-menopausal women relative to pre-menopausal women [19, 20]. In line with our results, OSA is known to be among the strongest risk factors for OSA, with over half of all OSA diagnoses being linked to an individual being overweight [21]. OSA rates have been found to be positively correlated with BMI [22], and one group reported that a 10% increase in weight was associated with a 32% increase in AHI scores, thus contributing to more severe OSA [23]. Obesity is thought to contribute to OSA incidence both through reductions in lung volume and increases in fat deposition within the neck and other soft tissue regions [24]. Other factors that can influence OSA development include changes in the neural compensatory mechanisms responsible for maintaining airway patency, respiratory control system instability, and decreased functional residual capacity [25]. The implementation of more effective weight loss strategies is thus critical to reduce the incidence of OSA in the general population.

With respect to comorbidities, HTN has been linked to OSA risk in several reports [15, 26–29]. Both SBP and DBP are reportedly positively correlated with AHI values and negatively correlated with nadir nocturnal oxygen saturation [30]. DM is also commonly associated with OSA, with the Wisconsin Sleep Cohort Study have demonstrated an independent association between DM and OSA [31]. The mechanistic basis for this relationship may be that DM can impact OSA-related periodic breathing [32], although further research is necessary to fully understand how interactions between HTN, DM, and other conditions can affect OSA incidence.

Bouloukaki et al. previously reported that blood biomarkers may be of value when assessing individual risk of OSA [33], and OSA biomarker screening in high-risk populations has been linked to significant improvements in sleep specialist referrals and associated patient outcomes [34]. As such, our predictive model included Cr, BUN, SUA, and TG as blood biomarkers. SUA in particular has been previously identified as an independent predictor of OSA incidence, with each 1 mg/dL rise in SUA concentrations being associated with a 16% increase in OSA risk. Consistently, SUA was independently associated with OSA severity in a large study of OSA patients without known comorbidities [33], and there is evidence to suggest that hyperuricemia may promote oxidative stress and endothelial dysfunction, thereby favoring OSA development [35].

Multiple models capable of predicting OSA risk have been reported to date. For example, James et al. analyzed 370 participants and developed a predictive model with AUC values ranging from 0.669–0.757

based upon AHI [36]. Seon Tae Kim et al. employed a logistic regression analysis approach to establish two predictive models with AUC values of 0.782 and 0.809 [37], while Do-Yang Park et al. used a large-scale study to develop two models with and without physical examination data yielding respective AUC values of 0.835 and 0.839, respectively, although they did not analyze blood biomarkers in their model [38]. Relative to some of these previously proposed predictive models, ours had a higher AUC value, and our internal validation results exhibited excellent consistency among patient cohorts.

The nomogram developed herein (Fig. 2) is a simple tool that relies upon complex statistical models to enable the efficient quantification of personal OSA risk in a clinical setting. Vertical lines are drawn from the appropriate point on each clinical variable scale to the corresponding 'points' scale, after which all points values were summed, and another vertical line was drawn from the 'total points' scale to the 'Risk of OSA' scale in order to establish patient risk. For example, for a male patient (42 points) with obesity (52 points) and an SUA \geq 416 $\mu\text{mol/L}$ (55 points), this nomogram predicted an OSA risk value of 0.58. Overall, this nomogram can aid in the identification of individuals at a high risk of OSA, supporting early intervention. Importantly, all of the variables that compose this predictive model are both objective and easily analyzed such that this model can be readily utilized to screen for OSA risk in the general population.

However, there are still several limitations in our study. This is a cross-sectional study with a small sample size and single center, which could not represent all the Chinese population. In addition, although the authenticity of our model was affirmed by internal validation, external validation could not be conducted. Therefore, this prediction model needs to be further verified by a longitudinal, multicenter and large sample study.

Conclusions

In this study, we developed an OSA prediction model using LASSO analysis, included eight readily available variables. After verification, the model has good authenticity and practicability, and can be used to screen the high-risk population of OSA and carry out early intervention.

Abbreviations

OSA: obstructive sleep apnea; PSG: Polysomnography; AHI: apnea-hypopnea index; BMI: body mass index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; Cr: creatinine; SUA: serum uric acid; SBP: systolic blood pressure; DBP: diastolic blood pressure; HTN: hypertension; DM: diabetes mellitus; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride; γ -GGT: γ -glutamyltransferase; LASSO: least absolute shrinkage and selection operator; AUC: area under curve; ROC: receiver operating characteristic.

Declarations

Funding information

None

Author contributions

TMY carried out the conceptualization, investigation, data analysis, and wrote the first draft of the manuscript.

ZXS participated in investigation, data analysis, writing the first draft.

MMW participated in the investigation, data analysis, and verification.

RJZ participated in the conceptualization, investigation, review and revision.

MLH participated in the conceptualization, investigation and review and revision

All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

Ethics approval and consent to participant

The study was performed in accordance with the guidelines of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Institutional Review Board of Ningbo Yinzhou No2. Hospital.

Consent for publication

Not applicable

Data availability statement

All data are fully available without restriction.

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Figures

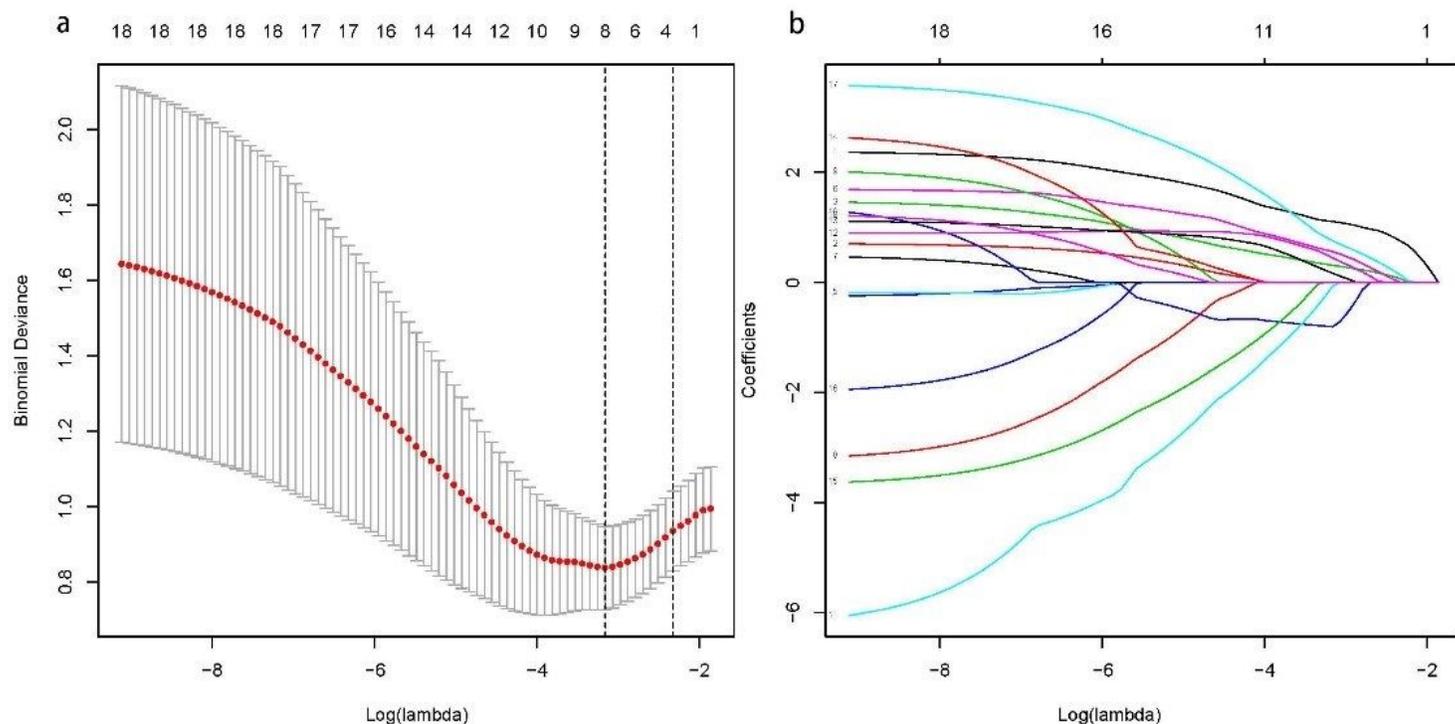


Figure 1

Feature selection using the LASSO regression model. (a) Optimal parameter (lambda) selection in the LASSO model used cross-validation via minimum criteria. The partial likelihood deviance (binomial deviance) curve was plotted versus $\log(\lambda)$. Dotted vertical lines were drawn at the optimal values by using the minimum criteria and the 1 SE of the minimum criteria. (b) LASSO coefficient profiles of the 18 features. A coefficient profile plot was produced against the $\log(\lambda)$ sequence. Vertical line was drawn at the value selected using fivefold cross-validation, where optimal lambda resulted in 8 features with nonzero coefficients.

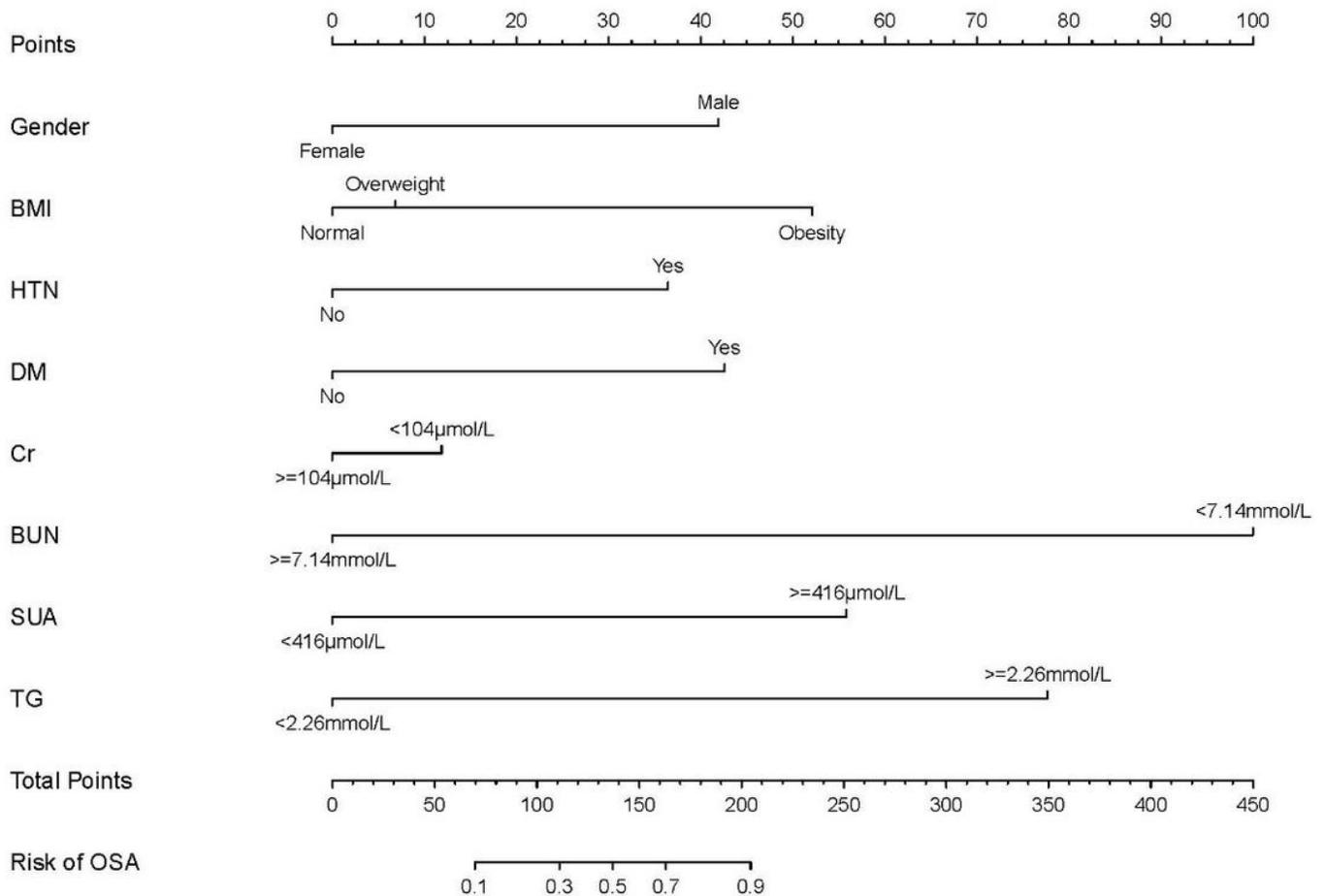


Figure 2

The predictive nomogram of OSA.

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