Development and validation of a nomogram for predicting the risk of obstructive sleep apnea in patients with type 2 diabetes

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Background: Obstructive sleep apnea (OSA) is highly prevalent among patients with type 2 diabetes mellitus (T2DM) in China, but few patients with clinical symptoms of OSA are referred for diagnostic polysomnography (PSG). Thus, this study aimed to develop and validate an easy-to-use nomogram that predicts the severity of OSA in patients with T2DM.

Methods: This retrospective study included consecutive patients with T2DM admitted to the Endocrinology Department, Third Affiliated Hospital of Soochow University between January 1, 2016 and December 31, 2019. OSA was diagnosed with PSG. Participants were randomly assigned to a training cohort (70%) and a validation cohort (30%). Demographic, anthropometric, and biochemical data were collected. A least absolute shrinkage and selection operator (LASSO) regression model was used to reduce data dimensionality and identify factors for inclusion in the nomogram (training cohort). Nomogram validation was performed in the validation cohort.

Results: The study included 280 participants in the training group and 118 participants in the validation group. OSA prevalence was 58.5%. LASSO regression identified waist-to-hip ratio (WHR), smoking status, body mass index (BMI), serum uric acid (UA), the homeostasis model assessment insulin resistance index (HOMA-IR), and history of fatty liver disease as predictive factors for inclusion in the nomogram. Discrimination and calibration in the training group (C-index =0.88) and validation group (C-index =0.881) were good. The nomogram identified patients with T2DM at risk for OSA with an area under the curve of 0.851 [95% confidence interval (CI), 0.788–0.900].

Conclusions: Our nomogram could be used to facilitate individualized prediction of OSA risk in patients with T2DM and help prioritize patients for diagnostic PSG.

Keywords: Obstructive sleep apnea (OSA); type 2 diabetes mellitus (T2DM); risk; nomogram

Introduction

Obstructive sleep apnea (OSA) is a disorder characterized by upper airway obstruction during sleep that results in breathing pauses, intermittent hypoxia, and fragmented sleep (1,2). The estimated prevalence of OSA in the general population is 9–38%, and the disorder is more common in men, older people, and those with higher body mass index (BMI) (3). Although a lower OSA prevalence of 3–7% has been reported in China (4), this is likely an underestimate due to people being unaware that they have the disorder or not seeking treatment (5).

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OSA is a sleep and respiratory disorder with high incidence, which can cause damage to multiple system, leading to complications such as hypertension, coronary heart disease, arrhythmia, pulmonary arterial hypertension, stroke, metabolic syndrome and psychological abnormality (6). The pathogenesis was poorly defined. Impairment in upper airway anatomy is the mean cause of OSA. Other causes such as impaired upper airway muscle function and unstable respiratory control play a contributory role (7). Craniofacial shape, obesity, pulmonary function and ventilatory control, genetics and irregular blood glucose control are common risk factors for OSA (8). OSA should be subject to long-term, multidisciplinary treatment management. Obesity is an independent risk factor for OSA, so weight control is of vital importance. other treatments including diet control, strengthening exercise, quit drinking and smoking. Non-invasive positive airway pressure therapy is initial choice for adult OSA patients. An oral appliance that keeps the jaw forward during sleep and a surgery to enlarge the upper airway are other choices. While in the United States, hypoglossal nerve stimulation is an effective treatment for some patients with a body mass index (BMI) less than 32 kg/m^2 (9).

Previous research has indicated that short-term sleep deprivation and fragmentation can induce insulin resistance and that extremes of habitual sleep duration are associated with type 2 diabetes mellitus (T2DM) (10). Furthermore, there is strong evidence that OSA is associated with metabolic syndrome, T2DM, and diabetic renal disease (11-14). It has been proposed that sleep fragmentation and chronic intermittent hypoxia result in the activation of the sympathoadrenal system, elevated oxidative stress, systemic inflammatory responses, and changes in adipokine levels that increase the risk of T2DM (15-17). Notably, the prevalence of OSA among outpatients with T2DM in China was found to be around 60–67%, and many of these cases had not been previously diagnosed (18,19).

Severe OSA is associated with significantly higher risks of cardiovascular disease, major adverse cardiovascular outcomes, stroke, sudden cardiac death, and all-cause mortality (20), highlighting the importance of the early diagnosis and management of OSA. A definitive diagnosis of OSA relies on polysomnography (PSG) (21); however (22), as this is an expensive and labor-intensive technique that is not widely available, patient access to PSG is limited and many patients with OSA remain undiagnosed. A variety of questionnaires have been developed for use in triage to predict the risk of OSA and thus identify high-risk patients that need referral for PSG, but these approaches are recognized to have limitations (23,24). Different questionnaires focus on different aspects, leading to different sensitivities. Alternative approaches to screening for OSA have included nomograms based on clinical data such as symptom history, demographic characteristics, anthropometric measurements, biochemical investigations, and spirometry data (25-27). obesity is a risk factor for OSA, therefore there was an article using a nomogram to study the incidence of OSA in obese patients (28). However, no previous studies have developed a nomogram tailored for use in patients with T2DM.

The aim of our study was thus to construct and validate an easy-to-use nomogram based on a constellation of objective demographic, biochemical, and anthropometric parameters that could be used to accurately predict the risk of OSA in patients with T2DM. It was anticipated that this nomogram could be used in the clinic to reduce the number of missed OSA diagnoses in patients with T2DM by identifying patients at high risk of OSA who should be referred for PSG. We present the following article in accordance with the TRIPOD reporting checklist (available at http://dx.doi.org/10.21037/atm-20-6890).

Methods

Study design and participants

This retrospective study included consecutive patients with T2DM admitted to the Endocrinology Department, Third Affiliated Hospital of Soochow University, Changzhou, China between January 1, 2016 and December 31, 2019. The diagnosis of T2DM was made in accordance with the American Diabetes Association (ADA) criteria (29). The exclusion criteria were the following: (I) prior diagnosis or treatment of OSA, (II) severe congestive heart failure, (III) severe pulmonary disease, (IV) severe chronic kidney disease, (V) severe hepatic disease, and (VI) pregnancy. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The protocol was approved by the Ethics Committee of the Third Affiliated Hospital of Soochow University. Written informed consent was obtained from each participant before inclusion in the study.

Sleep evaluation

All participants underwent full-night PSG using the Voyager Digital Imaging E-series system (Compumedics,

Melbourne, Australia). OSA was diagnosed according to an apnea-hypopnea index (AHI) ≥5 (21,30).

Collection of clinical data

The age and sex of each participant were recorded. Patients who smoked at least 1 cigarette per day during the study were regarded as smokers. Waist circumference was measured at the level of the umbilicus, hip circumference was measured at the level of maximum extension of the hip, and the waist-to-hip ratio (WHR) was determined from these values. BMI was calculated by dividing weight in kilograms by the square of height in meters. Blood pressure was measured with a mercury sphygmomanometer after the patient had been seated quietly for at least 10 min. A participant was considered to have hypertension if their blood pressure was >140/90 mmHg or if they were taking any anti-hypertensive drugs. Venous blood samples were obtained in the morning after an overnight fast, and standard laboratory procedures were used to measure the following biochemical parameters: alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), serum creatinine (CR), fasting C-peptide (FCP), fasting plasma glucose (FPG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), and uric acid (UA). The presence/absence of fatty liver was determined based on the medical history and ultrasonography. The homeostasis model assessment 2 insulin resistance index (HOMA2-IR) was calculated using software downloaded from http://www.dtu.ox.ac.uk.

Statistical analysis

The analysis was conducted using R 3.6.1.3 (TUNA Team, Tsinghua University, China), SPSS 24.0 (IBM, Armonk, NY, USA) and SAS 9.2 (SAS Institute, Cary, NC, USA). A random number table generated by SAS 9.2 was used to randomly assign 70% of the participants to the training cohort and 30% of the participants to the validation cohort. The logistic regression model was used to estimate the hazard ratio and corresponding [95% confidence interval (CI)] for risk factors. Selection methods (forward and exclusion criteria of type I error =0.1 based on likelihood ratio tests) were considered in the multivariate model to build the risk prediction model. P values were two-sided, and values of <0.05 were considered statistically significant. We used the glmnet package in R

to perform least absolute shrinkage and selection operator (LASSO) logistic regression, which is suitable for high-dimensional, low-sample size data with collinearity issues. Significant factors identified by LASSO regression were used to construct a nomogram to identify patients at risk of OSA (31). Validation was carried out using 1,000 bootstrap replications. Calibration diagrams were assessed as described in a previous report (32). The predictive and discriminatory ability of this model were evaluated by calculation of an index measuring the probability of concordance between the predicted and actual outcomes (C-index) (33). Model calibration was assessed based on Copas's proposal (34) of using a regression smoothing method to produce calibration plots that graphically describe the relationship between the observed and predicted probabilities of OSA. A two-sided P value <0.05 was considered statistically significant.

Results

Clinical characteristics of the study participants

Among the 414 patients screened for inclusion, 16 patients were excluded because they did not undergo PSG. Therefore, a total of 398 patients (279 men, 70.1%) were included in the final analysis. The clinical characteristics of the study participants are summarized in *Table 1*. The overall prevalence of OSA was 58.5%. Among the patients with OSA, the sleep disorder was considered to be severe in 45.5%, moderate in 29.6%, and mild in 24.9%. A total of 280 participants (70%) were randomly assigned to the training cohort, and 118 participants (30%) were assigned to the validation cohort. There were no significant differences between the training and validation cohorts in demographic and clinical characteristics. However, when compared with patients without OSA, patients with OSA had a higher proportion of males; a higher proportion of smokers; a greater prevalence of fatty liver; a higher BMI; a larger hip circumference; a larger waist circumference; a greater WHR; higher levels of AST, LDH, FCP, TG, and UA; a lower level of HDL; and a greater HOMA2-IR (P<0.05 for all parameters in both the training and validation cohorts; *Table 1*). Additional significant differences between patients with OSA and those without OSA were observed for prevalence of hypertension (validation cohort), TC (validation cohort), and AST (training cohort). In the training group, univariate analysis and multivariate analysis were performed to identify the risk factors associated with OSA in type 2 diabetes patients (*Table 2*).

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Table 1 Clinical characteristics of the study participants

Variable	Training group (n=280)			Validation group (n=118)		
	Non-OSA (n=116)	OSA (n =164)	P value	Non-OSA (n=49)	OSA (n=69)	P value
Gender			0.0174			0.0211
Male	74 (63.79)	126 (76.83)		27 (55.10)	52 (75.36)	
Female	42 (36.21)	38 (23.17)		22 (44.90)	17 (24.64)	
Fatty liver			<0.0001			0.0022
Yes	68 (58.62)	145 (88.41)		34 (69.39)	63 (91.30)	
No	48 (41.38)	19 (11.59)		15 (30.61)	6 (8.70)	
Smoke			<0.0001			<0.0001
Yes	15 (12.93)	71 (43.29)		1 (2.04)	31 (44.93)	
No	101 (87.07)	93 (56.71)		48 (97.96)	38 (55.07)	
Hypertension			0.1921			0.0052
Yes	78 (67.24)	122 (74.39)		32 (65.31)	60 (86.96)	
No	38 (32.76)	42 (25.61)		17 (34.69)	9 (13.04)	
Age (years)	51.35±12.09	52.08±12.95	0.6354	51.24±14.05	52.32±10.97	0.6423
BMI (kg/m^2)	24.37±2.88	28.39±3.96	<0.0001	24.53±3.48	28.59±3.89	<0.0001
DBP (mmHg)	85.75±9.93	85.40±11.57	0.7913	86.92±10.53	86.26±10.96	0.7448
HC (cm)	96.09±6.30	101.52±7.48	<0.0001	94.78±5.75	101.91±9.10	<0.0001
Height (cm)	167.29±8.30	170.01±7.38	0.0043	166.57±8.15	169.00±7.37	0.0941
SBP (mmHg)	140.51±18.31	138.47±18.39	0.3604	138.78±15.79	141.42±15.72	0.3705
WC (cm)	87.45±7.20	97.49±11.94	<0.0001	86.45±8.14	97.88±10.30	<0.0001
Weight (kg)	68.41±10.76	82.17±13.30	<0.0001	68.08±10.82	82.05±14.67	<0.0001
WHR	0.91±0.05	0.96±0.09	<0.0001	0.91±0.06	0.96±0.06	<0.0001
AHI (U/L)	2.50 (1.80, 3.30)	23.80 (12.10, 44.45)	<0.0001	2.30 (1.65, 2.80)	29.10 (17.90, 46.40)	<0.0001
ALT (U/L)	23.00 (17.00, 34.00)	28.00 (20.00, 46.50)	0.0091	22.00 (17.00, 35.00)	32.00 (19.00, 46.00)	0.0727
AST (U/L)	14.00 (12.00, 19.00)	20.00 (16.00, 30.00)	<0.0001	14.00 (12.00, 18.00)	20.00 (15.00, 28.00)	0.0006
BUN (mmol/L)	4.86 (3.86, 6.11)	5.12 (4.10, 6.10)	0.4200	4.89 (3.99, 6.00)	5.19 (4.14, 6.00)	0.8063
CR (mmol/L)	72.00 (61.95, 82.15)	71.00 (63.00, 81.00)	0.9148	66.00 (56.00, 77.00)	73.00 (62.00, 85.70)	0.0598
FCP (mmol/L)	1.39 (1.01, 1.96)	2.47 (1.80, 3.31)	<0.0001	1.41 (1.16, 2.08)	2.55 (1.90, 3.45)	<0.0001
FPG (mmol/L)	9.55 (7.70, 12.04)	9.11 (7.02, 11.40)	0.0816	9.20 (7.90, 10.70)	9.37 (7.86, 12.50)	0.3343
GGT (mmol/L)	32.50 (22.00, 52.00)	36.00 (23.00, 60.50)	0.3436	34.00 (23.00, 49.00)	38.00 (23.00, 71.00)	0.4064
HDL (mmol/L)	1.06 (0.89, 1.18)	0.95 (0.82, 1.09)	0.0003	1.12 (0.95, 1.18)	0.95 (0.81, 1.03)	0.0001
HOMA-IR	1.33 (1.02, 1.89)	2.16 (1.58, 2.73)	<0.0001	1.37 (1.03, 1.91)	2.16 (1.78, 2.83)	<0.0001
LDH (mmol/L)	140.50 (122.00, 166.00)	181.00 (159.50, 206.00)	<0.0001	137.00 (121.00, 173.00)	187.00 (158.00, 206.00)	<0.0001
LDL (mmol/L)	2.29 (1.98, 2.84)	2.38 (1.93, 2.78)	0.5701	2.63 (2.01, 3.18)	2.17 (1.78, 2.75)	0.0513
TC (mmol/L)	4.65 (4.13, 5.31)	4.66 (3.95, 5.17)	0.7161	4.84 (4.22, 5.51)	4.38 (3.81, 5.22)	0.0425

Table 1 (*continued*)

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Variable	Training group (n=280)			Validation group (n=118)		
	Non-OSA (n=116)	OSA (n =164)	P value	Non-OSA (n=49)	OSA (n=69)	P value
TG (mmol/L)	1.90 (1.44, 3.06)	2.46 (1.82, 3.97)	0.0003	2.08 (1.45, 2.86)	2.71 (1.82, 3.90)	0.0083
UA (mmol/L)	242.55 (202.75, 296.55)	326.00 (267.65, 393.15)	<0.0001	235.10 (198.30, 285.80)	335.80 (274.70, 395.90)	<0.0001

Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage). Baseline characteristics were compared between the two groups using the t-test for independent samples (normally distributed continuous variables), Mann-Whitney U test (non-normally distributed continuous variables), or chi-squared test or Fisher's exact test (categorical variables). OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CR, creatinine; DBP, diastolic blood pressure; FCP, fasting C-peptide; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; HC, hip circumference; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDH lactate dehydrogenase; LDL low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, cholesterol; TG, triglycerides; UA, uric acid; WC, waist circumference; WHR, waist-to-hip ratio.

Table 2 Risk factors for OSA in type 2 diabetic patients according to the logistic regression model

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
WHR	518,994.834	3,891.605–69,214,534.6	<0.001	22,435.245	19.925–25,224,295.12	0.005
Smoke	5.141	2.754–9.595	<0.001	1.812	0.8–4.102	0.154
Gender	0.531	0.315–0.898	0.018	0.699	0.316–1.545	0.376
Age	1.005	0.986–1.024	0.634	NA		
Hypertension	1.415	0.839–2.387	0.193	NA		
BMI	1.453	1.315–1.606	<0.001	1.29	1.142–1.458	<0.001
AST	1.083	1.048–1.118	<0.001	1.147	1.06–1.242	<0.001
GGT	1.002	0.997–1.008	0.397	NA		
TC	1.01	0.797–1.282	0.932	NA		
TG	1.261	1.085–1.465	0.002	1.011	0.852–1.2	0.899
HDL	0.172	0.056–0.53	0.002	0.908	0.318–2.593	0.857
LDL	0.906	0.629–1.305	0.596	NA		
CR	1.003	0.989–1.017	0.665	NA		
UA	1.015	1.011–1.019	<0.001	1.008	1.002–1.014	0.00497
HOMA-IR	2.279	1.643–3.16	<0.001	1.300	0.886–1.907	0.17972
HbA1c	0.825	0.742–0.918	<0.001	0.966	0.88–1.061	0.47126
Fatter liver	5.387	2.944–9.858	<0.001	2.321	0.967–5.57	0.05953

OSA, obstructive sleep apnea; NA, not available; WHR, waist-to-hip ratio; BMI, body mass index; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; TC, cholesterol; TG, triglycerides; HDL, high-density lipoprotein cholesterol; LDL low-density lipoprotein cholesterol; CR, creatinine; UA, uric acid; HOMA-IR, homeostasis model assessment of insulin resistance.

Factor selection for the predictive model

The LASSO method is a shrinkage estimation method that can be used to select relevant features in high-dimensional data. Compression coefficients are obtained by constructing a penalty function, and some of the compression coefficients are set to zero to establish a more refined linear regression
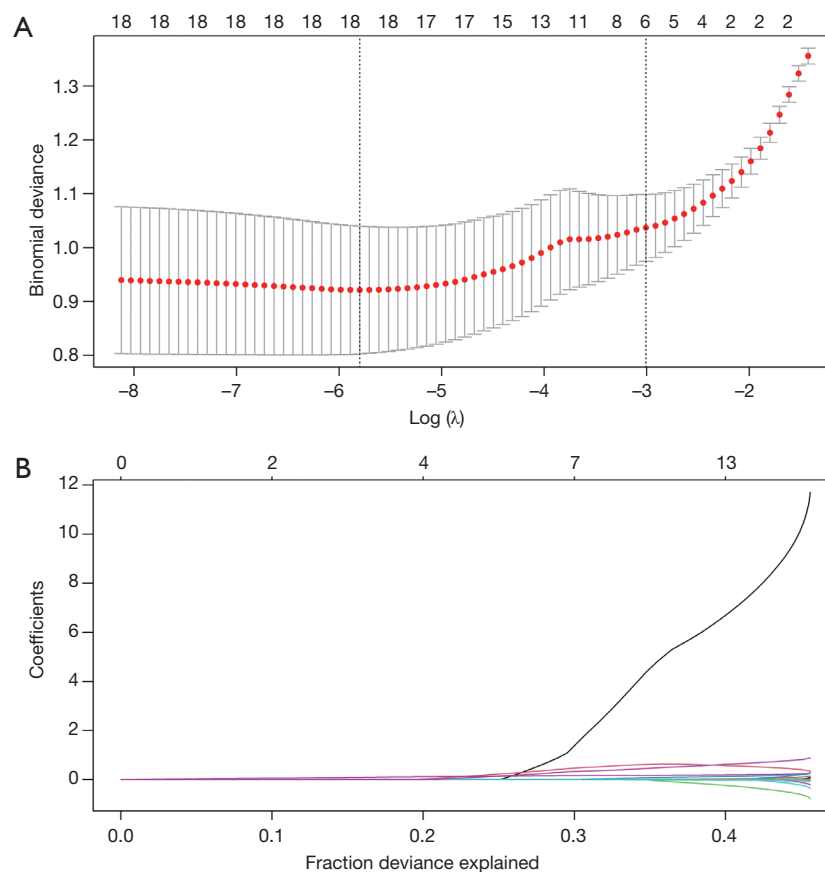
Figure 1 LASSO feature selection model. (A) LASSO coefficients of 17 candidate variables. (B) Identification of the optimal penalization coefficient (λ) in the LASSO model was achieved by 10-fold cross-validation and the minimum criterion. The left vertical line represents the minimum error, and the right vertical line represents the cross-validated error within 1 standard error of the minimum. LASSO, least absolute shrinkage and selection operator.

model. In this study, a risk score was calculated from a linear combination of factors weighted by their coefficients, and a coefficient profile plot was constructed (*Figure 1A*). A cross-validated error plot of the LASSO regression model is shown in *Figure 1B*. The most regularized and parsimonious model, with a cross-validated error within 1 standard error of the minimum, included 6 of the 17 variables which were significantly different between two groups. Therefore, a model incorporating 6 independent predictors (WHR, smoking status, BMI, UA, HOMA2-IR, and history of fatty liver) was developed into a simple-to-use nomogram (*Figure 2*).

Validation of the nomogram

A 1,000 bootstrap analysis was used to validate the nomogram. The C-index for predicting OSA in patients with T2DM was 0.88 in the training group and 0.88 in the validation group. Since both C-index values exceeded 0.7, the model was deemed suitable and sufficiently accurate for predicting OSA in patients with T2DM. The calibration plots revealed an excellent correlation between observed and predicted OSA in both the training group (*Figure 3A*) and validation group (*Figure 3B*).

LASSO feature regression model

A LASSO feature regression model was established to directly visualize the differences between OSA and non-OSA (*Figure 4*). According to the nomogram, the cutoff point for distinguishing between OSA and non-OSA was 94.43. Therefore, the nomogram score for each participant was standardized using the following formula: standardized
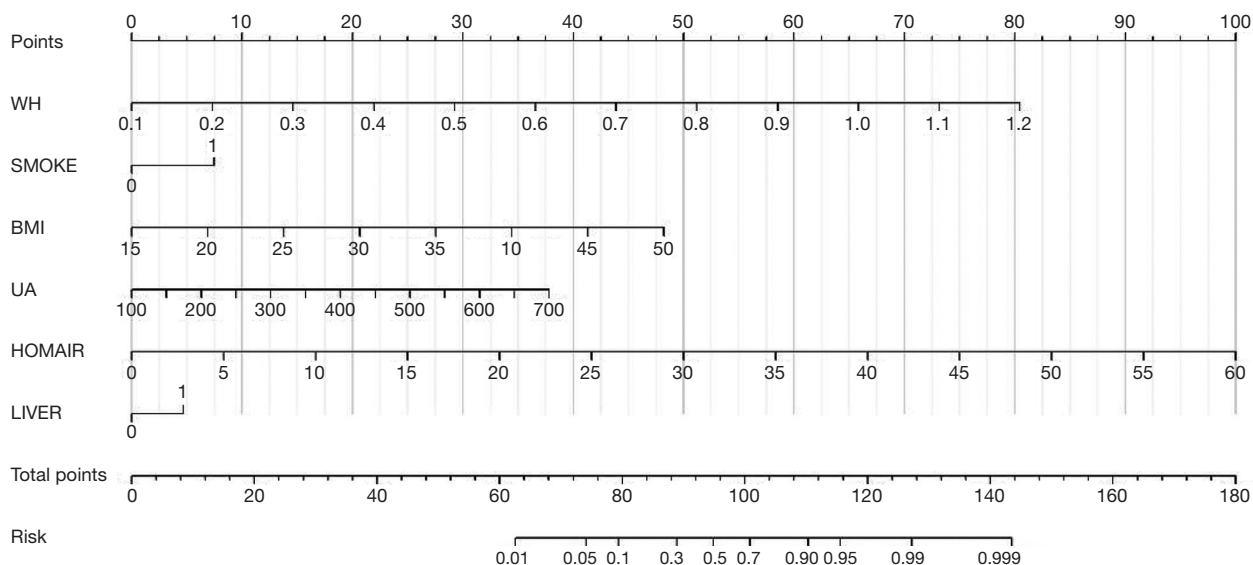
Figure 2 Nomogram constructed for predicting OSA in patients with type 2 diabetes mellitus. OSA, obstructive sleep apnea; BMI, body mass index; HOMA-IR, homeostasis model assessment 2 insulin resistance index; LIVER, history of fatty liver; SMOKE, smoking status; UA, uric acid; WHR, waist-to-hip ratio.
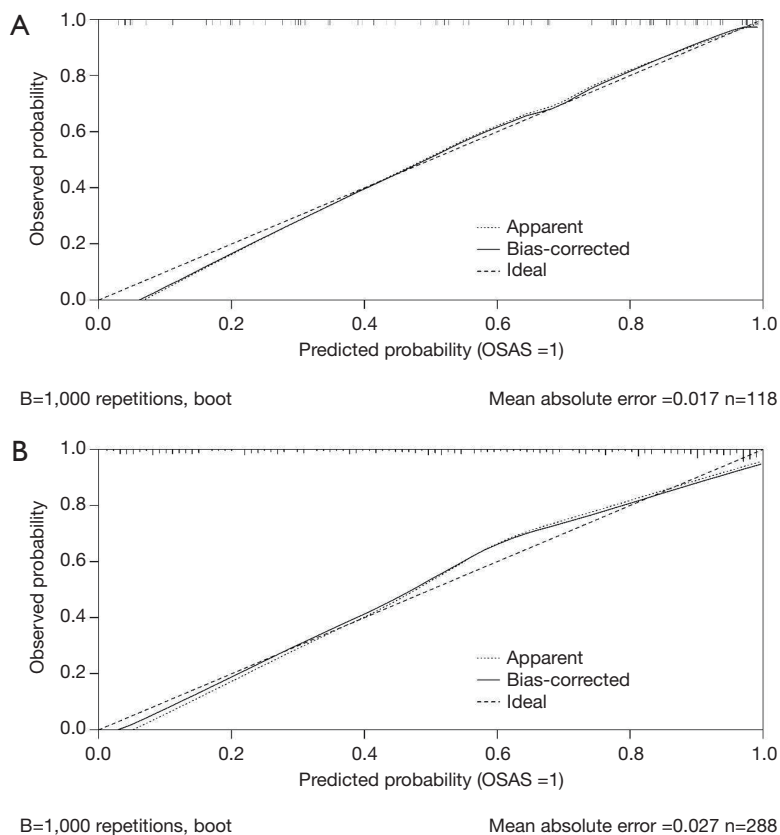

Figure 3 Calibration curves for the nomogram. (A) Calibration curve for the nomogram in the training group. (B) Calibration curve for the nomogram in the validation group.
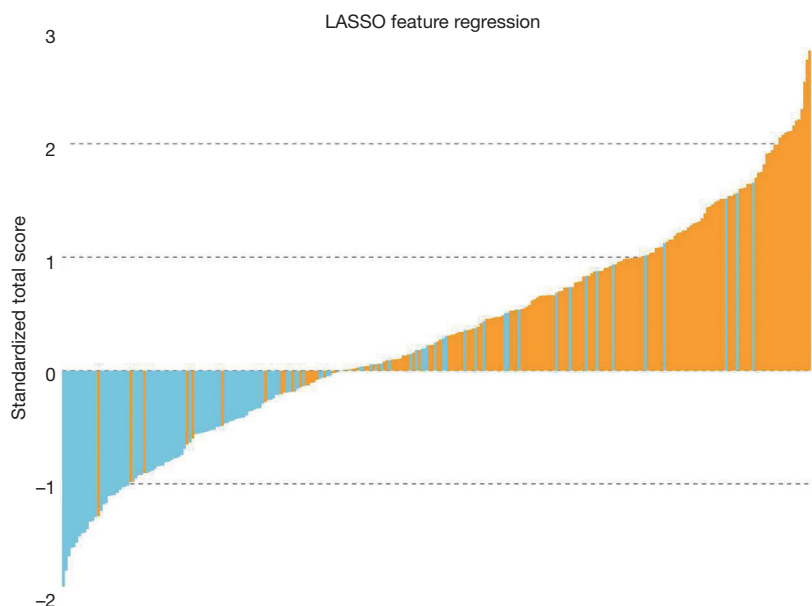
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Figure 4 LASSO feature regression. Standardized total score for each participant in the training group. The y-axis represents the calculated value, and the x-axis represents each patient. Green bars represent scores for patients with type 2 diabetes mellitus who do not have obstructive sleep apnea, and red bars represent scores for patients with type 2 diabetes mellitus who do have obstructive sleep apnea. LASSO, least absolute shrinkage and selection operator.

Table 3 The clinical utility of the nomogram in the detection of obstructive sleep apnea

Apnea-hypopnea index	Area under the curve	Sensitivity	Specific	Positive likelihood ratio	Negative likelihood ratio	Positive predictive value	Negative predictive value
15> AHI ≥5	0.855 (0.794–0.904)	83.93 (71.7–92.4)	78.45 (69.9–85.5)	3.89 (2.7–5.6)	0.20 (0.1–0.4)	65.3 (53.1–76.1)	91.0 (83.6–95.8)
30> AHI ≥15	0.874 (0.810–0.922)	88.57 (73.3–96.8)	75.00 (66.1–82.6)	3.54 (2.5–5.0)	0.15 (0.06–0.4)	51.7 (38.4–64.8)	95.6 (89.1–98.8)
>30	0.905 (0.854–0.943)	86.30 (76.2–93.2)	80.17 (71.7–87.0)	4.35 (3.0–6.3)	0.17 (0.10–0.3)	73.3 (62.6–82.2)	90.3 (82.9–95.2)

score = (nomogram score – 94.43)/standard deviation. Since our study included more participants with OSA than participants without OSA, this resulted in the accumulation of colored blocks in the figure. Therefore, we randomly selected 164 patients with both T2DM and OSA and 116 patients with T2DM but without OSA to establish the LASSO feature regression model (*Figure 4*).

Clinical utility of the nomogram in the prediction of OSA, moderate-to-severe OSA, and severe OSA

Receiver operating characteristic (ROC) curve analysis was used to evaluate the utility of the nomogram in the prediction of modest OSA (15> AHI ≥5), moderate-to-

severe OSA (30> AHI ≥15) and severe OSA (AHI ≥30) in patients with T2DM. The area under the curve (AUC) values at the optimal diagnostic cutoff points were 0.851 for predicting OSA, 0.868 for predicting moderate-to-severe OSA, and 0.907 for predicting severe OSA (*Table 3*), indicating that the nomogram performed well.

An example of nomogram usage

To illustrate the use of the nomogram, here we provide an example of a patient with the following clinical characteristics: active smoker, history of fatty liver, waist circumference =96 cm, hip circumference =100 cm, WHR =0.96, height =172 cm, weight =80 kg, BMI =27.04 kg/m^2, UA

=240.7 µmol/L, FPG =4.37 mmol/L, FCP =531.6 pmol/L, and HOMA2-IR =1.12. By applying the above values to the nomogram, a total score of 102.37 was obtained, which corresponded to a 72% probability of having OSA.

Discussion

To our knowledge, this is the first study to develop an easy-to-use nomogram that predicts the risk of OSA in patients with T2DM. The nomogram developed using data from the training group incorporates 6 items, namely WHR, smoking status, BMI, UA, HOMA2-IR, and history of fatty liver. Furthermore, validation demonstrated that the nomogram has good accuracy and discriminatory ability. Our novel nomogram could be used at the bedside or in an outpatient setting to perform a rapid assessment of OSA risk and help identify patients that would normally be referred for diagnostic PSG, which is a more costly and time-consuming examination. The widespread use of this nomogram in patients with T2DM could potentially avoid unnecessary PSG examinations, thereby reducing the burden on patients and healthcare services.

The 17 candidate variables initially used for construction of the nomogram were reduced to 6 potential predictors using the LASSO regression method. The LASSO regression technique is suitable for analyzing large sets of clinical factors and avoids overfitting (35). Our nomogram suggests that smoking, obesity, and disordered glucose metabolism may be good predictors of OSA in patients with T2DM. Tobacco smoking may increase the severity of OSA through alterations in sleep architecture, upper airway neuromuscular function, and arousal mechanisms, as well as induction of upper airway inflammation (36). Although smoking cessation might be expected to improve OSA, the evidence to support this is limited (37); hence, ex-smokers may still be at higher risk of OSA. Nonalcoholic fatty liver disease (NAFLD) is closely associated with metabolic syndrome, which appears to be a driving force for a multitude of comorbidities such as insulin resistance and OSA (38). OSA is highly prevalent in patients with metabolic syndrome (39), and an increasing severity of OSA is associated with poorer control of T2DM, hypertension, and dyslipidemia, all of which are components of metabolic syndrome (40). Obesity is considered an important risk factor for OSA, and several large-scale studies have concluded that an increase in BMI is associated with an increasing prevalence and severity of OSA (41-43). Medical treatments and bariatric surgery to achieve weight loss have been shown to alleviate OSA severity, thereby confirming a cause-effect relationship between these two disorders (44). Furthermore, insulin resistance is a key factor in the pathogenesis of T2DM and other OSA-associated metabolic perturbations. In patients with OSA and T2DM, the effects of sleep-disordered breathing on glucose metabolism and the underlying mechanisms have yet to be thoroughly investigated. Nevertheless, in agreement with the findings of our study, previous research has demonstrated that severe OSA is associated with higher HOMA-IR (45).

Several questionnaires have been developed with the aim of identifying patients at high risk of OSA who should be prioritized for PSG, such as the Berlin questionnaire, the Rome questionnaire, and the BASH'IM score, but these tools appear to have inadequate sensitivity or specificity (23,46,47). Three-dimensional cone-beam computerized tomographic airway analysis has also been evaluated as a tool to study the presence and severity of OSA, but this is not widely used because of its high cost (48). Kolotkin *et al.* constructed an alternative prediction model in patients with OSA undergoing bariatric surgery, but the sensitivity and specificity of this model were not high in the validation group (49). Magalang *et al.* utilized overnight pulse oximetry to improve the precision of a prediction model, but this method was time-consuming and labor intensive (50). Improvements in statistical modeling have resulted in the development of nomograms to assess OSA risk based on clinical syndromes, demographic characteristics, and anthropometric measures, and these approaches have been demonstrated to have reasonably good accuracy. Luo *et al.* utilized an ordinal logistic regression procedure to establish a nomogram encompassing numerous subjective variables and found that the discriminatory accuracy of this nomogram for non-OSA, moderate-severe OSA, and severe OSA was 83.8%, 79.9%, and 80.5%, respectively (25). Xu *et al.* used a LASSO regression technique to construct a nomogram that incorporated 8 independent factors (age, sex, glucose, apolipoprotein B, insulin, BMI, neck circumference, and waist circumference) and predicted non-OSA, moderate-to-severe OSA, and severe OSA with an accuracy of 77%, 80%, and 79%, respectively (26).

Whereas the populations enrolled in previous studies comprised participants suspected of having OSA, the present study specifically recruited patients with T2DM because this population is known to have a high prevalence of OSA. Since endocrinologists encounter a large number of patients with T2DM, there is a window of opportunity to screen patients with T2DM on endocrinology wards

for various comorbidities, including OSA, and implement appropriate interventions as necessary. The nomogram developed in this study performed well as a screening tool to identify patients with T2DM at risk of OSA, as demonstrated by AUC values >0.8. The 6-factor nomogram was established using a LASSO model to reduce overfitting, and calibration plots demonstrated excellent correlation between the predicted and observed probabilities of OSA. We believe that this nomogram could be an effective screening tool to identify patients with T2DM who are at high risk of OSA and thus should be referred for PSG.

This study has some limitations that should be taken into account when interpreting the data. First, the training group and validation group were recruited from the same single center, so whether or not these findings can be generalized to other populations is not clear. It will be important to validate our nomogram at other institutions in China and abroad before it can be widely implemented in clinical practice. Second, the construction of our nomogram was based only on demographic, anthropometric, and biochemical parameters, and other variables such as genetic factors were not considered. Third, the high prevalence of OSA in our study population may have affected the evaluation of the predictive parameters. Fourth, the inclusion of biochemical parameters makes the use of this nomogram somewhat more complex and time-consuming than simple questionnaires. Nevertheless, since routine measurement of these biochemical parameters is far more straightforward than PSG, improving the predictive accuracy of the nomogram by including these biochemical parameters likely outweighs the disadvantage of performing these blood tests.

The present study has established a novel nomogram to predict the risk of OSA in patients with T2DM admitted to an endocrinology ward. Although the sensitivity and specificity of this nomogram need further evaluation in the general population, we anticipate that this nomogram could be used as a screening tool to identify patients with T2DM who are at risk for OSA and thus merit referral for PSG.

Acknowledgments

Footnote

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