A Novel Clinical Tool to Detect Severe Obstructive Sleep Apnea Hypopnea Syndrome

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Research Article

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Abstract

Background: Obstructive sleep apnea hypopnea syndrome (OSAHS) is a disease with high morbidity and is associated with adverse health outcomes. Screening potential severe OSAHS patients will improve the quality of patient management and prognosis, while the accuracy and feasibility of existing screening tools are not so satisfactory. The purpose of this study is to develop and validate a well-feasible clinical predictive model for screening potential severe OSAHS patients.

Methods: We performed a retrospective cohort study including 1,920 adults with overnight polysomnography among which 979 cases were diagnosed with severe OSAHS. Based on demography, symptoms, and hematological data, a multivariate logistic regression model was constructed and cross-validated and then a nomogram was developed to identify severe OSAHS. Moreover, we compared the performance of our model with two most commonly used screening tools, Epworth sleepiness scale (ESS) and Stop-Bang Questionnaire (SBQ), among patients who completed the questionnaires.

Results: Severe OSAHS was associated with male, BMI≥ 27 kg/m^2, high blood pressure, choke, sleepiness, apnea, white blood cell count ≥ 9.5×10^9/L, hemoglobin ≥ 175g/L, triglycerides ≥ 1.7 mmol/L. The AUC of the final model was 0.75 (95% CI: 0.67-0.82), with sensitivity and specificity under the optimal threshold selected by maximizing Youden Index of 71% and 68%. Among patients having the information of ESS or SBQ, the AUC of our model was statistically significantly greater than that of ESS (0.74 vs 0.58, *P*=0.006) and not less than that of SBQ (0.78 vs 0.66, *P*=0.073).

Conclusion: Based on common clinical examination on admission, we develop a novel model and a nomogram for identifying severe OSAHS from inpatient with suspected OSAHS, which provides physicians with a visual and easy-to-use tool for screening severe OSAHS.

Introduction

Patients with obstructive sleep apnea hypopnea syndrome (OSAHS) usually have recurrent hypoxemia, hypercapnia and microarousal, which leads to sleep fragmentation, poor sleep quality. Severe OSAHS is defined as the Apnea Hypopnea Index (AHI)≥ 30 events per hour, which is obtained by overnight polysomnography (PSG).[1] It is estimated that 425 million patients are moderate to severe OSAHS.[2] OSAHS leads to huge economic and social burden while most of these burden are caused by severe OSAHS.[3, 4]

Severe OSAHS brings several short and long-term health consequences from perioperative complications to uncontrolled hypertension, stroke, fatal and nonfatal cardiovascular events, or even death. [5–7] The intervention strength is quite different between mild, moderate and severe OSAHS according to most world-wide guidelines.[8, 9] Optimal blood pressure is difficult to control in patients with hypertensive severe OSAHS, and hypertension drug resistance rate is higher in the OSAHS population.[10] Severe OSAHS patients complicated by atrial fibrillation (AF) have a poor response to antiarrhythmic drugs and a higher incidence of AF recurrence. At the same time, the prevalence of OSAHS is high in surgical

population,[11] but up to 80% of severe OSAHS patients may still not be diagnosed.[12, 13] They may have unplanned admission to the intensive care unit (ICU) and prolonged hospitalization,[13] even a higher rate of postoperative reintubation.[14]

Therefore, the identification and treatment of high-risk patients with severe OSAHS in the surgical and non-surgical population may help to reduce medical expense and make individualized treatment.[2, 15]

Although polysomnography (PSG) is the gold standard for the diagnosis of OSAHS, it is expensive and time consumption and the evaluation is mostly limited to large medical centers.[16] Currently, the existing screening tools include Stop-Bang Questionnaire (SBQ), DES-OSA score, P-SAP score, Berlin questionnaire (BQ) and OSA50. Some symptom indicators in these screening tools are subjective and the measure of anthropometric indicators require relative professionalism skill, leading to unsatisfied feasibility and prediction performance.[17, 18] In addition, researchers had attempted to propose several other screening models based on small sample size. However, these models needed to measure with anthropometric indicators, upper airway pressure, nocturnal oximetry even and multivariate prediction rules developed by neural networks. All of them were difficult to be applied to non-sleep clinics.[19–21] Several studies showed elevated levels of systemic mediators of inflammation in OSAHS patients, including inflammatory markers such as intercellular adhesion molecule, c-reactive protein(CRP),[22] tumor necrosis factor (TNF),[23] IL-1, and IL-6.[23, 24] But all these were inflammatory markers not routinely used in daily clinical practice. Nevertheless, the vast information contained in hematological indexes is ignored by all of the existing models. Therefore, our severe OSAHS model included blood routine and biochemical indexes on the basis of routine demography and main complaint.

In this study, we aimed to develop a novel screening tool to identify high-risk patients with severe OSAHS. Our tool was based on demography, symptoms, and routine hematological items, which were friendly to general practitioners or surgeons. Furthermore, the predictive performances were compared between our tool and two most common screening tools (i. e. ESS and SBQ).

Patients And Methods

Research population

We enrolled adult patients who was admitted to Nan fang Hospital during the period from February 18, 2008 to January 21, 2019. All patients have undergone PSG due to suspected OSAHS. We used an intelligent database platform (Yi du Cloud Technology Ltd, Beijing, China) to identify patients eligible for this study. Data from the medical record system can be easily and safely exported to Microsoft Excel for next analysis. The patients were excluded if the important information of height, weight or AHI were missing due to the obstacles of data extraction in electronic medical system. We included several demographic indicators (age, sex, BMI, smoking and blood pressure), OSAHS-related symptoms and hematological indexes (blood routine, blood lipids and blood glucose). Blood was drawn from patients on an empty stomach for more than 8 hours and sent for examination in time.

Sleep monitoring method

The polysomnography monitoring device included electroencephalogram (EEG), electromyogram (EMG), electrocardiogram (ECG), thermistor and nasal pressure sensor for oral and nasal air flow, chest band and abdominal band for breathing, pulse oxygen saturation measurement, microphone for snoring collection and sensor for sleeping position. The airflow of oral and nasal breathing disappeared or weakened obviously during sleep, and the duration ≥ 10 seconds were defined as apnea. Hypopnea was defined as a decrease of more than 30% in oral and nasal air flow compared to the baseline level during sleep, accompanied by a decrease in blood oxygen saturation of more than 3% or with micro-arousal for a duration of ≥ 10 seconds. The apnea hypopnea index (AHI) was calculated by the ratio of apnea and hypopnea events to total sleep time. According to the guidelines by American Academy of Sleep Medicine,[1]AHI > 30/h was considered to be severe OSAHS.

Statistical analysis

All continuous variables were described by means and standard deviations (SD), and categorical variables were presented as counts and proportions. We compared means and proportions between groups by using Student's t test and Chi-Square test (or Fisher's exact test if appropriate), respectively. A nomogram was developed to predict severe OSAHS using demographics, symptoms and hematological examination of the patients in 2008–2018 and was cross-validated using data in 2019. In details, the nomogram was developed in three steps: (1) Examining the exposure-response relationship between each continuous variable and severe OSAHS by using restricted cubic splines function in the univariate logistic regression.[25, 26] If the relationship curve is generally linear, we only considered linear effect by adding the linear term of the factor in the following analyses. Otherwise, the continuous variable was classified into a dummy variable (normal or abnormal) according to the reference value range. (2) Fitting a full model including all variables under study. The multicollinearity problem was examined using the generalized variance inflation factor (GVIF). The $GVIF^{[1/(2\times df)]}$ for all variables in the model were less than 2.24 (i.e., $5^{[1/2]}$)[27]. (3) Developing a stepwise regression model with a backward selection procedure to obtain a simplified model that corresponded to the smallest Akaike information criterion.[28] (4) Constructing the nomogram based on the stepwise logistic regression model.

To evaluate the performance of the nomogram, we estimated the area under the receiver operator characteristic (ROC) curve (AUC).[29] Besides, the performance was also validated with bootstrap resampling repeated 1000 times and temporal validation.[28]Sensitivity, specificity and accuracy were calculated for the best cut-off values defined by maximum Youden index. The calibration was assessed by using a Hosmer-Lemeshow test and by comparing the predicted and observed probabilities of patients having severe OSAHS.[30]

Furthermore, the performance was compared with that of two other commonly used screening questionnaire (ESS and SBQ) among the patients who completed these questionnaires. The AUC and sensitivity and specificity was compared by DeLong test[29] and McNemar χ^2 test,[31] respectively. All

statistical analysis was performed using R (version 4.1.1). A value of two-tailed $P < 0.05$ was considered to be statistically significant.

Results

Study flow

The flow chart of this study is shown in Fig. 1. We extracted clinical data of 5,215 hospitalized patients who have underwent polysomnography. Study subjects without documentation of height, weight, AHI in their electronic medical records were excluded. A total of 1,920 eligible patients among which 979 patients (50.98%) were severe OSASH, were included in this study. The screening model was developed using the training dataset in 2008–2018 (n = 1,647, 86%) and validated using the temporal validation dataset in 2019 (n = 273, 14%).

Patient characteristics

Table 1 presents the basic characteristics of the patients. Among 1,920 patients, 85.8% were men and the average age was 49.67 years. Patients with BMI ≥ 27kg/m^2 and hypertension accounted for 49.94% and 34.79%, respectively. Patients with severe OSAHS were younger, fatter, sleepier, and had higher prevalence of smoking or hypertension than patients without severe OSAHS (P < 0.05).

Model development

In terms of the continuous variables, age, white blood cell count (WBC), red blood cells count (RBC), hemoglobin (Hb) and triglycerides (TG) showed a non-linear relationship with the patient's risk of developing severe OSAHS (e Fig. 1, e Fig. 2, e Fig. 3), therefore they were converted into categorical variables in the multivariate analyses. The level of serum glucose and cholesterol shows general linear relationship with the risk of severe OSAHS.

The full model including all variables except total cholesterol, which was deleted because of its overhigh GVIF (e Table 1), and the stepwise model had very similar diagnostic accuracy (e Table 2). To simplify the model and facilitate its application, the stepwise model was recommended as the final model, including gender, BMI, blood pressure, choke, sleepiness, apnea, white blood cell count, hemoglobin content and triglyceride. We found some other potential predictors (white blood cell count, hemoglobin and triglyceride content) which have been previously neglected. In the final model (Table 2), wight blood cell count ≥ 9.5×10^9/L, hemoglobin content ≥ 175g/L and triglycerides count ≥ 1.7mmol/L were significantly associated with an increased risk of getting severe OSAHS with an OR of 1.73 (95% CI: 1.15–2.59), 14.58 (95% CI: 1.86-114.51) and 1.45 (95% CI: 1.17–1.81), respectively. The risk of severe OSAHS in male was higher than that in female with an OR of 3.36 (95% CI: 2.27–4.99). The patients with BMI ≥ 27kg/m^2, hypertension, choke, sleepiness and apnea were more likely to be severe OSAHS, with OR of 3.40 (95% CI: 2.49–4.65), 1.68 (95% CI: 1.22–2.31), 1.59 (95% CI: 1.23–2.04), 1.96 (95% CI: 1.53–2.51) and 4.57 (95% CI: 2.04–10.22), respectively.

Based on the stepwise model, the nomogram is presented to provide a visualized easy-to-use tool for physicians (Fig. 2). In the nomogram, each value of a variable corresponds to a score, and the corresponding scores for the nine variables included in the model can be summed to achieve a total score for an individual. The total score is then projected onto a total point scale to obtain the probability of severe OSAHS for any individual according to his or her profile.

Model validation

For the training dataset, the AUC for the final model was 0.76 (95% CI:0.73–0.78). The sensitivity, specificity, and accuracy were 65.28%, 72.35% and 68.73%, respectively (e Table 2). The optimism-corrected AUC obtained from bootstrap resampling was 0.75 (e Fig. 4), suggesting good internal validation. In addition, the Hosmer-Lemeshow test indicated that the model calibrated well (P = 0.636), and the calibration curve showed that the predicted probabilities of severe OSA risk in general agreed well with the observed probabilities (e Fig. 5). For the validation dataset, the model also showed good performance with AUC of 0.73 (95% CI: 0.67–0.79) (e Fig. 6). Visual inspection of the calibration plots showed good agreement between the model predicted probabilities of severe OSA and actual risk (e Fig. 7) and the Hosmer-Lemeshow test indicated that the model calibrated well (P = 0.162).

Comparison with ESS and SBQ

167 patients including 97 severe patients who had the information of ESS were selected from 1,920 patients to compare the predictive performance of our model with ESS. The AUC of the new model was 0.74 (95% CI: 0.66–0.82), which was significantly better than 0.58 (95% CI: 0.49–0.67) of the ESS score (Fig. 3, Table 3). Under the optimal threshold obtained with the best Youden index, compared with ESS, our new model had significantly higher sensitivity and accuracy (53.61% vs 24.74%, 66.47vs 53.89%) but lower specificity (84.29% vs 94.29%) (Table 4).

Based on the data of 100 patients (56% were severe OSASH) who had the information of Stop Bang, the AUC was 0.78 (95% CI: 0.69–0.87) for the new model and 0.66 (95% CI: 0.56–0.77) for the Stop Bang method (Fig. 3, Table 3). What's more, for the optimal threshold, the specificity and accuracy of SBQ were 52.27% and 63.00%, respectively, relatively lower than our model (81.82% and 72.00%) while SBQ have higher sensitivity (71.43% vs 64.29%) (Table 4).

In practice, SBQ is a five-level ordinal scale. When using a score of 1, 2, 3, 4, 5 as the thresholds, the specificity was 0.00%, 25.00%, 52.27%, 79.55% and 97.73% and the sensitivity was 100.00%, 92.86%, 71.43%, 39.29% and 10.71%, respectively. Assumed the same or a little bit higher specificity achieved (i. e. 2.27%, 25.00%, 52.27%, 79.55% and 97.73%), our new model had a higher or the same sensitivity of 100.00%, 98.21%, 83.93%, 64.29% and 26.71%, respectively (e Table 3). ESS is a 0–24 scale. Given the same specificity obtained by the ESS method when using a score of 1 to 16, 23 and 24 as the threshold, our model has higher or the same sensitivity ranging from 53.61–100.00% and 6.19%. If the ESS method takes a value from 17–22 as the threshold, the ESS method has a specificity of more than 90% and a sensitivity of less than 30% although it was higher than our model (e Table 4).

Discussion

We constructed a statistical model for predicting severe OSAHS based on 1920 hospitalized Chinese patients extracted from the hospital electronic medical record system with guaranteed data quality. Further we provided a visual nomogram as an easy-to-use clinical screening tool accordingly. The nomogram requires only routinely collected information on admission (including gender, BMI, blood pressure, choke, sleepiness, apnea, WBC, hemoglobin, and triglyceride), but it still has a satisfactory performance in terms of discrimination and calibration. The sensitivity and specificity of our model were 71% and 68% respectively, and the model outperformed SBQ and ESS.

Although many screening tools and predictive models had been developed to identify high-risk patients with severe OSAHS, most of them had low performance. A meta-analysis mentioned that the pooled specificity levels of Berlin questionnaire (BQ), SBQ, and STOP ranged 28%~38%, which were lower than our model, although the pooled sensitivity levels of these tools were higher (84%~93%).[32] According to our result, the specificity and accuracy of SBQ were relatively lower than our model, but with higher sensitivity. The reason might be that Far-East Asian men were nonobese, despite the presence of severe OSAHS, which mean that Asian were more sensitive to BMI.[33] Nevertheless, the measurement of neck circumference in SBQ also required certain skill. In agreement with our findings, ESS seemed to be inferior to our model.[32] A relatively low specificity (36.2%) and high sensitivity (87.2%) were also reported for the American Society of Anesthesiologists checklist when applied in surgical patients in Canada.[34] Questionnaires, scale and checklist mentioned above tend to have a low specificity and more non severe OSAHS patients will be misdiagnosed,[35] which means that the time-consuming and expensive PSG would be applied to a certain number of healthy patients when these tools are used. At the same time, it would further lead to a waste of medical resources and patients' unwarranted panic and anxiety. Compared with these tools, our model has a relatively balanced sensitivity and specificity. Similarly, DES-OAS performed satisfactorily in differentiating between severe OSAHS and others, with a sensitivity and specificity of 89% and 65%, respectively among susceptible surgical patients in Belgium.[36] However, most of the items in aforementioned questionnaires, scale, and checklist are not routinely obtained partially due to that it is difficult to collect the information during a hospital visit. (e.g. thyromental distance,[37] thyroid-chin distance[38]) and some are subjective (e.g. degree of sleepiness,[39] degree of snoring[40]), resulting in patients-report bias of the clinic sample. Besides, it takes time to complete such a file and therefore it might be inefficient to screen severe OSAHS using these tools, especially for urgent cases.

A limited number of studies used statistical methods to predict severe OSAHS with less information (and most of which are professional) as compared with the questionnaires, scale and checklist mentioned above. Huang et al. applied a support vector machine (sensitivity: 70%, specificity: 70%) and a logistic regression model (sensitivity: 65%, specificity: 79%),[41] while Amra et al. used the decision tree algorithm to predict the severe OSAHS (sensitivity: 57%, specificity: 90%).[42] The performance of these models is comparable to our nomogram. Nevertheless, these models require data which are not commonly collected during a consultation in most non-otolaryngology departments (such as neck circumference

and waist circumference for the former and Mallampati indices for the later). Our model would be of more clinical significance in the screening of severe OSAHS, since all of the data needed are often obtained on admission.

To our knowledge, this is the first study using indices from routine blood tests for the screening of severe OSAHS. We found that patients with ≥ 9.5 $\times 10^9$/L WBC counts were more likely to be severe OSAHS compared with those with WBC counts ranging from 3.5 to 9.5 $\times 10^9$/L. Similarly, a study reported that the severity of OSA might be positively associated with WBC counts.[43] In addition, our findings suggested that patients with a high level of hemoglobin (≥ 175 g/L) were at an elevated risk of severe OSAHS. Patients with severe OSAHS are chronically hypoxic. Hypoxia can induce inflammation and cause a compensatory increase in hemoglobin, therefore high levels of WBC and hemoglobin would be predictors of severe OSAHS.

Our results show that rising triglyceride to 1.7 mmol/L increases the risk of OSAHS. Previous studies have shown that OSAHS is independently associated with cardiovascular risk factors, such as hypertension and dyslipidemia.[44]Consistent with previous studies, we observed that males, high BMI, high blood pressure, choke, sleepiness, and apnea were predictors of severe OSAHS.[1]

Our study had some limitations. First, although we collected data from 1920 patients, only 167 patients had information of ESS and 100 patients had the information of Stop-Bang. The relatively small sample size may explain the statistically non-significant difference between Stop-Bang and our model with the optimal thresholds. Nevertheless, in terms of point estimation of sensitivity, specificity and accuracy, our model is not inferior to SBQ, and has better clinical maneuverability. Besides, when the specificity of our model is equal to the specificity of 79.55% for SBQ, the sensitivity obtained is significantly higher than SBQ. Second, we did not perform external validation for the model since no data were available for such an assessment. However, we did attempt internal validation and temporal validation in an effort to prevent data overinterpretation, and the result suggested satisfactory validation of the model. Third, some factors that may be related to OSAHS have not been considered, such as cardiovascular disease and ethnic differences. In view of these limitations, further efforts in forward-looking and multicenter data collection are encouraged to demonstrate the robustness of nomogram.

To sum up, demographical characteristics and indices obtained from routine blood tests can be used for screening the severe OSAHS. Our findings have important implications for identifying the severe OSAHS and improving the prognosis of surgical patients. Further studies are warranted to detect more predictors of severe OSAHS and thereafter to improve the predictive power of the nomogram.

Abbreviations

OSAHS= obstructive sleep apnea hypopnea syndrome; ESS=Epworth sleepiness scale; SBQ=Stop-Bang Questionnaire; BMI=body mass index; AUC=receiver operator characteristic curve; AHI=Apnea Hypopnea Index; PSG=polysomnography; AF=atrial fibrillation; ICU=intensive care unit; BQ=Berlin questionnaire;

CRP=c-reactive protein; TNF=tumor necrosis factor; IL=Interleukin; EEG=electroencephalogram; EMG=electromyogram; ECG=electrocardiogram; SD=standard deviations; GVIF=generalized variance inflation factor; ROC=receiver operator characteristic; WBC=white blood cell count; RBC=red blood cells count; Hb=hemoglobin; TG=triglycerides; HBP=high blood pressure; OR=odds ratio; SBP= systolic blood pressure; DBP= diastolic blood pressure; HDL-C= high density lipoprotein cholesterol; LDL-C= low density lipoprotein cholesterol; VLDL-C= very low density lipoprotein cholesterol; PPV = Positive Predictive Value; NPV = Negative Predictive Value; CI= confidence interval; TC = Total cholesterol

Declarations

Ethical Approval and Consent to participate

The data obtained has been approved by Nanfang Hospital of Southern Medical University.

Consent for publication

Not Applicable. The original data comes from Yidu Cloud Technology database platform and hides the patient's personal privacy information.

Availability of supporting data

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All of the author had no potential conflicts of interest exist with any companies/organizations.

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Authors' contributions

HH, YQ and CQ contributed to the study design. YQ, YS, SM, JM and LL contributed to data collection. ZL and CQ cleaned the data and performed dada analyses. YQ and ZL drafted the manuscript. All authors contributed to the interpretation of data, critical revision of the final manuscript, and approval of the final manuscript.

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References

1. Berry RB, Brooks R, Gamaldo C, Harding SM, Lloyd RM, Quan SF, Troester MT, Vaughn BV: **AASM Scoring Manual Updates for 2017 (Version 2.4)**. *J CLIN SLEEP MED* 2017, **13**(05):665–666.
2. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, Nunez CM, Patel SR, Penzel T, Pépin J *et al*: **Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis**. *The Lancet Respiratory Medicine* 2019, **7**(8):687–698.
3. Skaer TL, Sclar DA: **Economic implications of sleep disorders**. *PHARMACOECONOMICS* 2010, **28**(11):1015–1023.
4. Tarasiuk A, Reuveni H: **The economic impact of obstructive sleep apnea**. *CURR OPIN PULM MED* 2013, **19**(6):639–644.
5. Shafazand S: **Guideline: Insufficient evidence exists on screening for obstructive sleep apnea in asymptomatic adults**. *ANN INTERN MED* 2017, **166**(10):C50.
6. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V: **Obstructive sleep apnea as a risk factor for stroke and death**. *N Engl J Med* 2005, **353**(19):2034–2041.
7. Adderley NJ, Subramanian A, Toulis K, Gokhale K, Taverner T, Hanif W, Haroon S, Thomas GN, Sainsbury C, Tahrani AA *et al*: **Obstructive Sleep Apnea, a Risk Factor for Cardiovascular and Microvascular Disease in Patients With Type 2 Diabetes: Findings From a Population-Based Cohort Study**. *DIABETES CARE* 2020, **43**(8):1868–1877.
8. Randerath W, Bassetti CL, Bonsignore MR, Farre R, Ferini-Strambi L, Grote L, Hedner J, Kohler M, Martinez-Garcia MA, Mihaicuta S *et al*: **Challenges and perspectives in obstructive sleep apnoea: Report by an ad hoc working group of the Sleep Disordered Breathing Group of the European Respiratory Society and the European Sleep Research Society**. *EUR RESPIR J* 2018, **52**(3).
9. Lim DC, Pack AI: **Obstructive Sleep Apnea: Update and Future**. *ANNU REV MED* 2017, **68**:99–112.
10. Thunstrom E, Manhem K, Rosengren A, Peker Y: **Blood Pressure Response to Losartan and Continuous Positive Airway Pressure in Hypertension and Obstructive Sleep Apnea**. *Am J Respir Crit Care Med* 2016, **193**(3):310–320.
11. Chan MTV, Wang CY, Seet E, Tam S, Lai HY, Chew EFF, Wu WKK, Cheng BCP, Lam CKM, Short TG *et al*: **Association of Unrecognized Obstructive Sleep Apnea With Postoperative Cardiovascular Events in Patients Undergoing Major Noncardiac Surgery**. *JAMA* 2019, **321**(18):1788.
12. Singh M, Liao P, Kobah S, Wijeysundera DN, Shapiro C, Chung F: **Proportion of surgical patients with undiagnosed obstructive sleep apnoea**. *Br J Anaesth* 2013, **110**(4):629–636.
13. Finkel KJ, Searleman AC, Tymkew H, Tanaka CY, Saager L, Safer-Zadeh E, Bottros M, Selvidge JA, Jacobsohn E, Pulley D *et al*: **Prevalence of undiagnosed obstructive sleep apnea among adult surgical patients in an academic medical center**. *SLEEP MED* 2009, **10**(7):753–758.

14. Kaw R, Chung F, Pasupuleti V, Mehta J, Gay PC, Hernandez AV: **Meta-analysis of the association between obstructive sleep apnoea and postoperative outcome**. *Br J Anaesth* 2012, **109**(6):897–906.
15. Singh M, Liao P, Kobah S, Wijeysundera DN, Shapiro C, Chung F: **Proportion of surgical patients with undiagnosed obstructive sleep apnoea**. *BRIT J ANAESTH* 2013, **110**(4):629–636.
16. Gozal D: **Serum, urine, and breath-related biomarkers in the diagnosis of obstructive sleep apnea in children: is it for real?** *CURR OPIN PULM MED* 2012, **18**(6):561–567.
17. Deflandre E, Piette N, Bonhomme V, Degey S, Cambron L, Poirrier R, Brichant J, Joris J: **Comparison of clinical scores in their ability to detect hypoxemic severe OSA patients**. *PLOS ONE* 2018, **13**(5):e196270.
18. Senaratna CV, Perret JL, Lowe A, Bowatte G, Abramson MJ, Thompson B, Lodge C, Russell M, Hamilton GS, Dharmage SC: **Detecting sleep apnoea syndrome in primary care with screening questionnaires and the Epworth sleepiness scale**. *MED J AUSTRALIA* 2019, **211**(2):65–70.
19. Abrishami A, Khajehdehi A, Chung F: **A systematic review of screening questionnaires for obstructive sleep apnea**. *Canadian Journal of Anesthesia/Journal canadien d'anesthésie* 2010, **57**(5):423–438.
20. Cheung K, Ishman SL, Benke JR, Collop N, Tron L, Moy N, Stierer TL: **Prediction of obstructive sleep apnea using visual photographic analysis**. *J CLIN ANESTH* 2016, **32**:40–46.
21. Roche N, Herer B, Roig C, Huchon G: **Prospective Testing of Two Models Based on Clinical and Oximetric Variables for Prediction of Obstructive Sleep Apnea**. *CHEST* 2002, **121**(3):747–752.
22. Shamsuzzaman ASM, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V, Somers VK: **Elevated C-Reactive Protein in Patients With Obstructive Sleep Apnea**. *CIRCULATION* 2002, **105**(21):2462–2464.
23. Minoguchi K, Tazaki T, Yokoe T, Minoguchi H, Watanabe Y, Yamamoto M, Adachi M: **Elevated production of tumor necrosis factor-alpha by monocytes in patients with obstructive sleep apnea syndrome**. *CHEST* 2004, **126**(5):1473–1479.
24. Roytblat L, Rachinsky M, Fisher A, Greemberg L, Shapira Y, Douvdevani A, Gelman S: **Raised interleukin-6 levels in obese patients**. *Obes Res* 2000, **8**(9):673–675.
25. Tammemagi CM, Pinsky PF, Caporaso NE, Kvale PA, Hocking WG, Church TR, Riley TL, Commins J, Oken MM, Berg CD *et al*: **Lung cancer risk prediction: Prostate, Lung, Colorectal And Ovarian Cancer Screening Trial models and validation**. *J Natl Cancer Inst* 2011, **103**(13):1058–1068.
26. Steyerberg EW, Mushkudiani N, Perel P, Butcher I, Lu J, McHugh GS, Murray GD, Marmarou A, Roberts I, Habbema JD *et al*: **Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics**. *PLOS MED* 2008, **5**(8):e165, e165.
27. Snee R: **"Some Aspects of Nonorthogonal Data Analysis, Part I**. *J QUAL TECHNOL* 1973, **5**(2):67–79.
28. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, Vickers AJ, Ransohoff DF, Collins GS: **Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration**. *ANN INTERN MED* 2015, **162**(1):W1-W73.

29. DeLong ER, DeLong DM, Clarke-Pearson DL: **Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach**. *BIOMETRICS* 1988, **44**(3):837–845.
30. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP: **Nomograms in oncology: more than meets the eye**. *LANCET ONCOL* 2015, **16**(4):e173-e180.
31. Trajman A, Luiz RR: **McNemar chi2 test revisited: comparing sensitivity and specificity of diagnostic examinations**. *Scand J Clin Lab Invest* 2008, **68**(1):77–80.
32. Chiu H, Chen P, Chuang L, Chen N, Tu Y, Hsieh Y, Wang Y, Guilleminault C: **Diagnostic Accuracy of the Berlin Questionnaire, STOP-Bang, STOP, and Epworth Sleepiness Scale in Detecting Obstructive Sleep Apnea: A Bivariate Meta-analysis**. *SLEEP MED REV* 2016, **36**:57–70.
33. Li KK, Kushida C, Powell NB, Riley RW, Guilleminault C: **Obstructive sleep apnea syndrome: a comparison between Far-East Asian and white men**. *LARYNGOSCOPE* 2000, **110**(10 Pt 1):1689–1693.
34. Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, Khajehdehi A, Shapiro CM: **Validation of the Berlin Questionnaire and American Society of Anesthesiologists Checklist as Screening Tools for Obstructive Sleep Apnea in Surgical Patients**. *ANESTHESIOLOGY* 2008.
35. Saldías PF, Gassmann PJ, Canelo LA, Uribe MJ, Díaz PO: **[Accuracy of sleep questionnaires for obstructive sleep apnea syndrome screening]**. *Rev Med Chil* 2018, **146**(10):1123–1134.
36. Deflandre E, Degey S, Brichant J, Donneau A, Frognier R, Poirrier R, Bonhomme V: **Pre-Operative Ability of Clinical Scores to Predict Obstructive Sleep Apnea (OSA) Severity in Susceptible Surgical Patients**. *OBES SURG* 2017, **27**(3):716–729.
37. Ramachandran SK, Kheterpal S, Consens F, Shanks A, Doherty TM, Morris M, Tremper KK: **Derivation and Validation of a Simple Perioperative Sleep Apnea Prediction Score**. *Anesthesia & Analgesia* 2010, **110**(4):1007–1015.
38. Deflandre E, Degey S, Brichant J, Poirrier R, Bonhomme V: **Development and Validation of a Morphologic Obstructive Sleep Apnea Prediction Score**. *Anesthesia & Analgesia* 2016, **122**(2):363–372.
39. Johns MW: **A new method for measuring daytime sleepiness: the Epworth sleepiness scale**. *Sleep (New York, N.Y.)* 1991, **14**(6):540.
40. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP: **Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome**. *ANN INTERN MED* 1999, **131**(7):485–491.
41. Huang W, Lee P, Liu Y, Chiang AA, Lai F: **Support vector machine prediction of obstructive sleep apnea in a large-scale Chinese clinical sample**. *SLEEP* 2020, **43**(7).
42. Amra B, Pirpiran M, Soltaninejad F, Penzel T, Fietze I, Schoebel C: **The prediction of obstructive sleep apnea severity based on anthropometric and Mallampati indices**. *J RES MED SCI* 2019, **24**(1):66.
43. Wu M, Zhou L, Zhu D, Lai T, Chen Z, Shen H: **Hematological indices as simple, inexpensive and practical severity markers of obstructive sleep apnea syndrome: a meta-analysis**. *J THORAC DIS* 2018, **10**(12):6509–6521.

44. Coughlin S: **Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome**. *EUR HEART J* 2004, **25**(9):735–741.

Tables

Table 1
Characteristics of demographics, symptoms and laboratory indexes for patients with or without severe OSAHS

Factor	All patients	Non-severe OSAHS	Severe OSAHS	P-value
	N = 1,920	N = 941	N = 979	
Age (years), mean (SD)	49.67 (12.42)	51.25 (12.94)	48.16 (11.71)	< 0.001
Gender = Male, No. (%)	1,648 (85.8)	731 (77.7)	917 (93.7)	< 0.001
BMI, No. (%)				< 0.001
< 18.5 kg/m2	20 (1.04)	18 (1.9)	2 (0.2)	
18.5–23.9 kg/m2	360 (18.75)	266 (28.3)	94 (9.6)	
24–26.9 kg/m2	581 (30.26)	317 (33.7)	264 (27.0)	
≥ 27 kg/m2	959 (49.94)	340 (36.1)	619 (63.2)	
Blood Pressure, No. (%)a				< 0.001
Normal	364 (18.95)	221 (23.5)	143 (14.6)	
Elevated	888 (46.25)	447 (47.5)	441 (45.0)	
Hypertension	668 (34.79)	273 (29.0)	395 (40.3)	
Smoking, No. (%)	422 (21.98)	187 (19.9)	235 (24.0)	0.033
Symptom, No. (%)				
Snore	1,199 (62.45)	520 (55.3)	679 (69.4)	< 0.001
Choke	1,162 (60.52)	471 (50.1)	691 (70.6)	< 0.001
Sleepiness	1,018 (53.02)	393 (41.8)	625 (63.8)	< 0.001
Apnea	65 (3.39)	14 (1.5)	51 (5.2)	< 0.001
Laboratory, mean (SD)				
White blood cell count, ×109/L	7.00 (1.91)	6.68 (1.90)	7.29 (1.82)	< 0.001
Red blood cell count, ×1012/L	5.02 (0.59)	4.87 (0.57)	5.16 (0.57)	< 0.001
Hemoglobin count, g/L	146.62 (16.00)	142.45 (15.09)	150.69 (14.55)	< 0.001
Neutrophil, %	55.78 (8.76)	55.73 (9.07)	55.82 (8.47)	0.812

a Normal: SBP < 120mmHg and DBP < 80mmHg; Elevated: SBP is 120mmHg and / or DBP is 80-89mmHg; Hypertension: SBP ≥ 140 and/or DBP ≥ 110mm.

OSAHS = obstructive sleep apnea hypopnea syndrome; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; VLDL-C = very low density lipoprotein cholesterol.

Factor	All patients	Non-severe OSAHS	Severe OSAHS	P-value
Triglycerides, mmol/L	2.69 (2.74)	2.39 (2.52)	2.99 (2.91)	< 0.001
Total cholesterol, mmol/L	5.00 (1.10)	5.00 (1.08)	5.01 (1.13)	0.886
HDL-C, mmol/L	1.03 (0.26)	1.04 (0.26)	1.02 (0.26)	0.137
LDL-C, mmol/L	3.16 (0.82)	3.17 (0.82)	3.14 (0.82)	0.439
VLDL-C, mmol/L	0.90 (0.91)	0.87 (0.82)	0.94 (1.00)	0.101
Blood glucose, mmol/L	5.89 (2.19)	5.99 (2.42)	5.80 (1.95)	0.066
a Normal: SBP < 120mmHg and DBP < 80mmHg; Elevated: SBP is 120mmHg and / or DBP is 80-89mmHg; Hypertension: SBP ≥ 140 and/or DBP ≥ 110mm.				
OSAHS = obstructive sleep apnea hypopnea syndrome; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; VLDL-C = very low density lipoprotein cholesterol.				

Data are presented as mean (SD) or No. (%) unless otherwise noted.

Table 2
Results of multivariate logistic regression models of clinical predictors for severe OSAHS

Predictors	Full Model		Simplified Model	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Gender				
Male vs Female	3.38 (2.26–5.05)	< 0.001	3.36 (2.27–4.99)	< 0.001
Age, year				
< 20	Reference	-	-	-
20–39	4.55 (0.46–44.57)	0.193	-	-
40–59	3.87 (0.40-37.67)	0.244	-	-
60–79	3.94 (0.40-38.78)	0.240	-	-
≥ 80	3.96 (0.35-45.00)	0.267	-	-
BMI, kg/m2				
18.5–23.9	Reference	-	Reference	-
< 18.5	0.39 (0.08–1.96)	0.255	0.39 (0.08–1.88)	0.238
24-26.9	1.48 (1.06–2.07)	0.021	1.47 (1.06–2.05)	0.022
≥ 27	3.43 (2.50–4.71)	< 0.001	3.40 (2.49–4.65)	< 0.001
Blood pressurea				
Normal	Reference	-	Reference	-
Elevated	1.25 (0.93–1.69)	0.145	1.26 (0.94–1.71)	0.125
Hypertension	1.67 (1.21–2.31)	0.002	1.68 (1.22–2.31)	0.001
Smoking				-
Yes vs No	0.85 (0.65–1.12)	0.252	-	
Snore				-
Yes vs No	1.04 (0.76–1.42)	0.816	-	
Choke				
Yes vs No	1.53 (1.16–2.02)	0.003	1.59 (1.23–2.04)	< 0.001
Sleepiness				

a Normal blood pressure: SBP < 120mmHg and DBP < 80mmHg; normal high value: SBP is 120-140mmHg and/or DBP is 80-89mmHg; High blood pressure: SBP ≥ 140 and/or DBP ≥ 110mm. See Table 1 legend for expansion of the abbreviation.

Predictors	Full Model		Simplified Model	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Yes vs No	1.95 (1.49–2.54)	< 0.001	1.96 (1.53–2.51)	< 0.001
Apnea				
Yes vs No	4.33 (1.92–9.75)	< 0.001	4.57 (2.04–10.22)	< 0.001
White blood cell count, ×109/L				
3.5–9.5	Reference	-	Reference	-
< 3.5	0.45 (0.11–1.88)	0.273	0.46 (0.11–1.88)	0.283
≥ 9.5	1.73 (1.12–2.66)	0.014	1.73 (1.15–2.59)	0.008
Red blood cell count, ×1012/L				
4.3–5.8	Reference	-	-	-
< 4.3	1.07 (0.64–1.79)	0.801	-	-
≥ 5.8	1.47 (0.93–2.33)	0.096	-	-
Neutrophil %	1.00 (0.99–1.01)	0.946	-	-
Hemoglobin count, g/L				
130–175	Reference	-	Reference	-
< 130	1.10 (0.70–1.75)	0.679	1.18 (0.81–1.73)	0.391
≥ 175	10.27 (1.28–82.42)	0.028	14.58 (1.86-114.51)	0.011
Triglycerides, mmol/L				
≥ 1.7 vs 0-1.7	1.45 (1.15–1.82)	0.001	1.45 (1.17–1.81)	0.001
LDL-C	0.94 (0.82–1.08)	0.374	-	-
HDL-C	0.79 (0.52–1.21)	0.275	-	-
VLDL-C	1.06 (0.93–1.22)	0.361	-	-
Blood glucose	0.99 (0.94–1.04)	0.743	-	-

a Normal blood pressure: SBP < 120mmHg and DBP < 80mmHg; normal high value: SBP is 120-140mmHg and/or DBP is 80-89mmHg; High blood pressure: SBP ≥ 140 and/or DBP ≥ 110mm. See Table 1 legend for expansion of the abbreviation.

Table 3
Comparison of the performance of three methods in predicting severe OSAHS

Model characteristics	AUC (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Accuracy (%) (95% CI)
ESS (N = 167)	0.58 (0.49–0.67)	24.74 (16.54–34.54)	94.29 (86.01–98.42)	53.89 (46.02–61.62)
The new model (N = 167)	0.74 (0.66–0.82)	53.61 (43.19–63.80)	84.29 (73.62–91.89)	66.47 (58.76–73.58)
P-value	0.006 [a]	< 0.001 [b]	0.096 [b]	0.013 [b]
Stop-Bang (N = 100)	0.66 (0.56–0.77)	71.43 (57.79–82.70)	52.27 (36.69–67.54)	63.00 (52.76–72.44)
The new model (N = 100)	0.78 (0.69–0.87)	64.29 (50.36–76.64)	81.82 (67.29–91.81)	72.00 (62.13–80.52)
P-value	0.073 [a]	0.540 [b]	0.009 [b]	0.233 [b]

CI = confidence interval; AUC = Area Under Receiver Operating Characteristic Curve.

Sensitivity, specificity and accuracy are derived from the best threshold which is obtained with the best Youden Index for each method. Under this threshold, the corresponding score was 2 and 6 for Stop-Bang and ESS, respectively.

[a] *P*-value for Delong test.

[b] *P*-value for McNemar test.

Figures

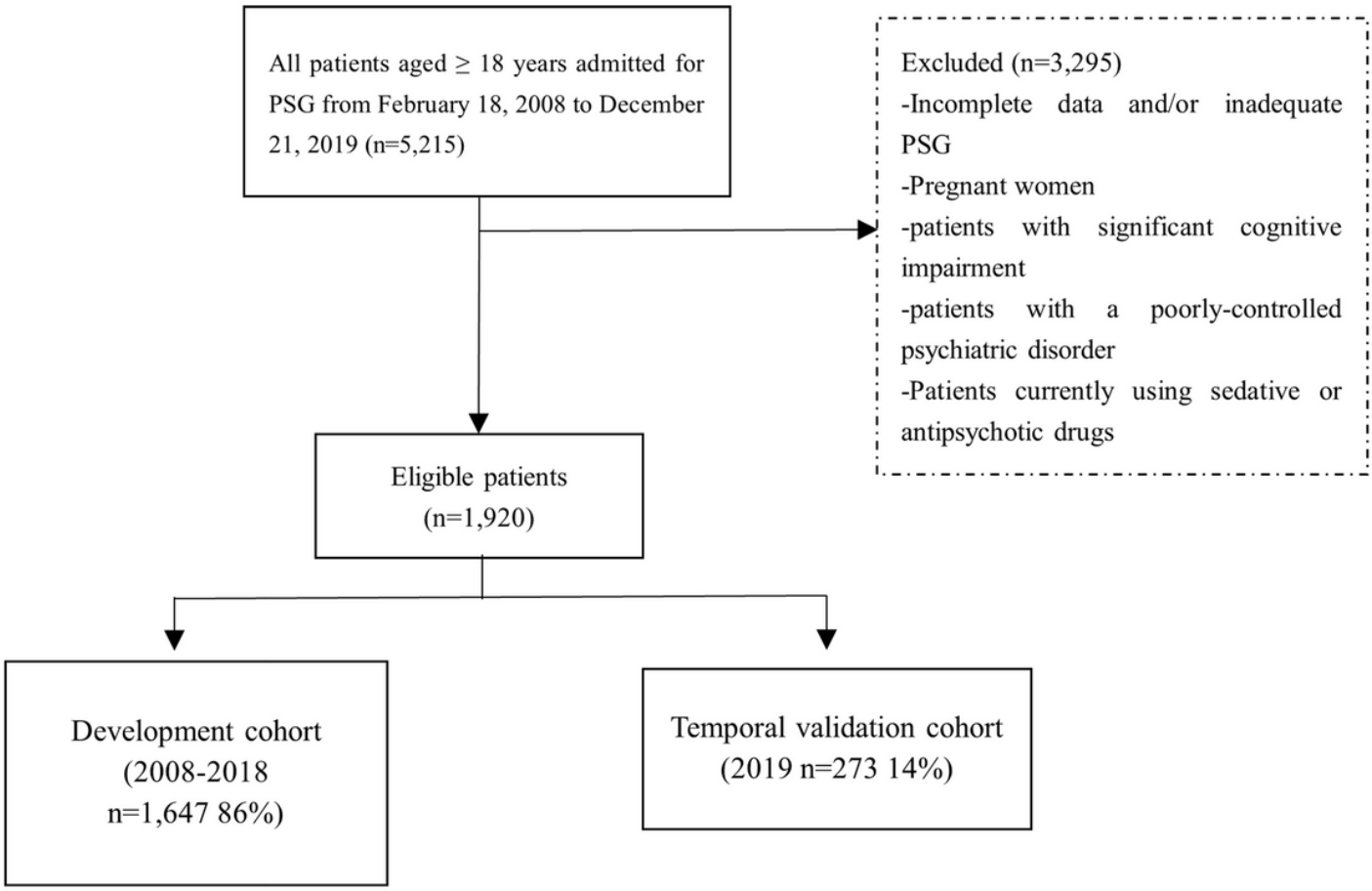

Figure 1

Study flow. PSG = polysomnography; AHI = apnea-hypopnea index

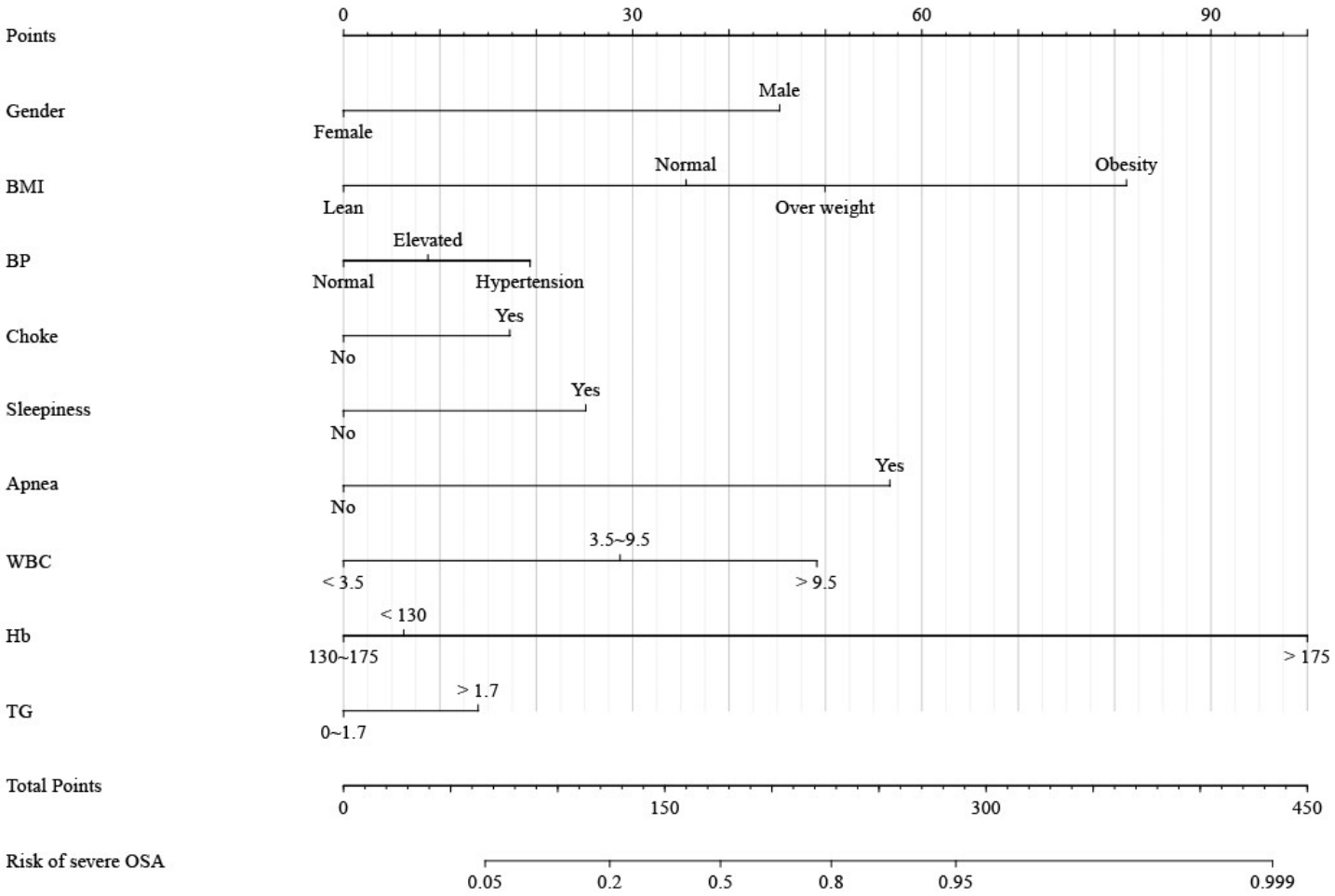

Figure 2

Nomogram of clinical predictive model for patients with severe OSAHS. Blood pressure (BP): Normal, SBP < 120mmHg and DBP < 80mmHg; Elevated, SBP is 120-140mmHg or DBP is 80-89mmHg; Hypertension, SBP ≧ 140 or DBP ≧ 110mm. BMI: Lean, < 18.5 kg/m^2; Normal, 18.5 ~ 23.9 kg/m^2; Over weight, 24 ~ 26.9 kg/m^2; Obesity, ≧ 27 kg/m^2. WBC = White blood cell count (×10^9/L); Hb = Hemoglobin (g/L); TG = Triglycerides (mmol/L)

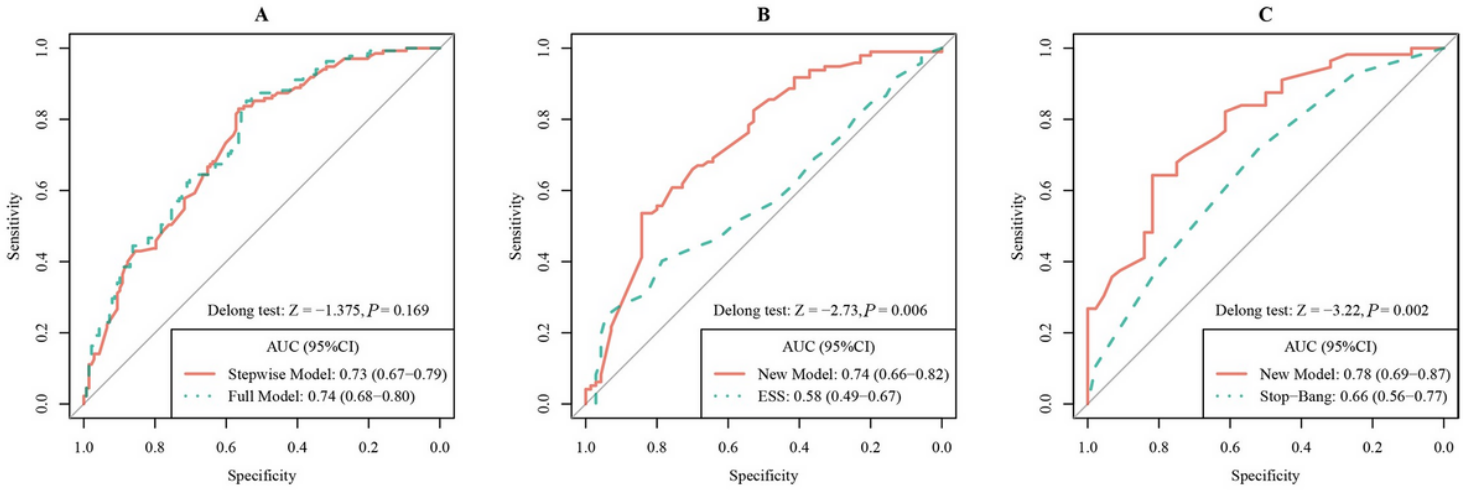

Figure 3

Legend not included with this version.

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