Age, Body Mass Index, and Daytime and Nocturnal Hypoxia as Predictors of Hypertension in Patients With Obstructive Sleep Apnea

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A growing body of evidence links obstructive sleep apnea (OSA) with hypertension. The authors performed a retrospective cohort study using the University Hospital of Larissa Sleep Apnea Database (1501 patients) to determine predictors of in-laboratory diagnosed OSA for development of hypertension. Differences in continuous variables were assessed via independent samples *t* test, whereas discrete variables were compared by Pearson's chi-square test. Multivariate analysis was performed via discriminant function analysis. There were several significant differences between hypertensive and normotensive patients. Age, body mass index, comorbidity, daytime oxygen saturation, and indices of hypoxia during sleep were deemed the most accurate predictors of hypertension, whereas apnea-hypopnea index and desaturation index were not. The single derived discriminant function was statistically significant (Wilk's lambda=0.771, χ^2=289.070, P<.0001). Daytime and nocturnal hypoxia as consequences of chronic intermittent hypoxia play a central role in OSA-related hypertension and should be further evaluated as possible severity markers in OSA. *J Clin Hypertens (Greenwich).* 2016;18:146–152.

Obstructive sleep apnea (OSA) is characterized by repetitive interruption of ventilation during sleep caused by collapse of the pharyngeal airway. The apnea-hypopnea index (AHI) is the number of apneas and hypopneas per hour of sleep and has been used to characterize the severity of the OSA syndrome (OSAS). A diagnosis of OSAS is accepted when a patient has an AHI >5 and associated symptoms (eg, excessive daytime sleepiness, fatigue, or impaired cognition) or an AHI ≥15 regardless of associated symptoms.[1,2]

OSA is a common condition of sleep-disordered breathing and occurs in approximately 5% to 10% of the general population, regardless of race and ethnicity.[3] It is estimated that 30% to 40% of hypertensive patients have OSA and 50% to 56% of OSA patients have hypertension.[4] An association between OSA and hypertension has been observed since the early description of OSA in the 1970s.[5–7] However, it had been difficult to clarify the cause-effect relationship between the two disorders. This is because patients with hypertension and patients with OSA have common risk factors such as age, sex, obesity, smoking, and alcohol abuse.[8–10] In recent years, there has been a large body of evidence estimating the role of OSA as an independent risk factor for hypertension. However, the results of these studies were controversial. Data from some studies support a dose-response relationship of OSA at baseline and the cumulative incidence of hypertension.[11,12] In contrast, other studies have reported that the unadjusted risk of hypertension increases in concert with AHI, but this association was not significant after adjustment for potential confounding variables.[13,14] Furthermore, the mechanisms underlying hypertension in patients with OSAS are still poorly understood. Intermittent hypoxia (defined as repetitive short cycles of desaturation followed by rapid re-oxygenation) is supposed to play a pivotal role in the cardiovascular disease process.[15–17]

Thus, we performed a retrospective cohort study to investigate the relationship between OSA and hypertension and find predictive factors of in-laboratory diagnosed OSA patients for development of hypertension.

METHODS

Study Population

We studied 1501 patients (50±15.2 years, 246 women) who complained of snoring or/and sleep interruption and excessive daytime sleepiness and had been consecutively referred to University Hospital of Larissa for investigations of possible OSA between January 2000 and December 2010. They underwent full standard in-laboratory polysomnography (PSG). We designed a database including patient demographics, clinical history, respiratory function data (spirometry), and finally all parameters included in their in-laboratory PSG. Patients (n=1227) with an AHI >5 and associated symptoms (eg, excessive daytime sleepiness, fatigue, or impaired cognition) were included in the final statistical analyses (Figure). Individuals with previously diagnosed respiratory failure of any etiology were excluded.

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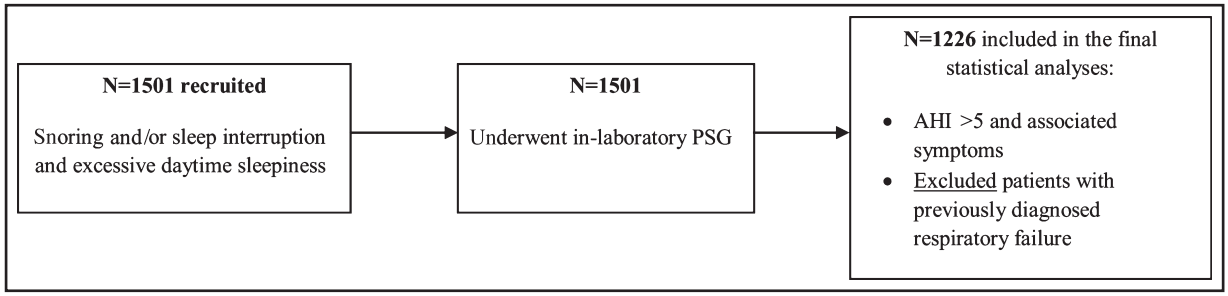

FIGURE. Flow diagram. PSG indicates polysomnography; AHI, apnea-hypopnea index.

Hypertensive patients were defined as individuals who were previously diagnosed as hypertensive and were also taking antihypertensive medication. The age-adjusted Charlson Comorbidity Index (CCI) score for each patient was calculated based on the algorithm formatted as Microsoft Excel Macro, developed by Hall and colleagues.[18] Comorbidity was determined as the concurrence of a disease included in and scored by the CCI criteria. Daytime mean oxygen saturation (SaO_2) was estimated as the average measurement of the pulse oximetry over an hour as the patient was awake, at rest, and in a sitting position. The study protocol and related procedures were approved by the institutional review board of the University Hospital of Larissa and the University of Thessaly Medical School.

Polysomnography

PSG included electroencephalography, electrooculography, submental electromyography, anterior tibialis electromyography, nasal cannula airflow signal using a nasal cannula/pressure transducer system, oral thermistor, electrocardiography, and body position. Sleep was scored manually according to the criteria of Rechtschaffen and Kales. Respiratory efforts were monitored with abdominal and thoracic bands. Arterial SaO_2 was measured using pulse oximetry. Arousals were scored according to standard criteria. Apnea was defined as complete cessation of airflow for at least 10 seconds in duration. Hypopnea was defined as one of the following three: (1) >50% reduction in airflow, (2) <50% reduction in airflow associated with a desaturation of >3%, or (3) a moderate reduction in airflow with associated arousal by electroencephalography. Apneas were classified as obstructive, central, or mixed according to the presence or absence of respiratory efforts.[1,2]

Statistical Analysis

Univariate Analyses. Demographic, clinical history, respiratory function data, and all parameters included in patients' in-laboratory PSG were expressed as mean±standard deviation for continuous variables and percentages for discrete variables. Univariate analysis was performed by independent samples *t* test and Pearson's chi-square for continuous and discrete variables, respectively. Data normality was assessed by the Kolmogorov-Smirnov test.

Multivariate Analyses. Multivariate analysis was performed via discriminant function analysis (DFA). Our study applied a linear discriminant model, a linear function of continuous predictor variables that best allocate subjects between c groups, where $c \geq 2$. Furthermore, the resulting function may be subsequently used to classify new cases. The discriminant formula for a population of [1, 2..., n] subjects, with [1, 2..., i] coefficients is described below,

$$D_j = A_j + k_1 m_{n1} + k_2 m_{n2} \ldots + k_i m_{ni}$$

where:

- "j" is the number of discriminant functions extracted, with $j \in [1, c\text{-}1]$.
- "D_j" is the discriminant function score for the jth discriminant function,
- "A" is the constant,
- "k_i" is the discriminant function coefficient,
- "m_{ni}" is the predictor variable value for the ith subject and the nth discriminant function coefficient.

The Wilk's lambda test is used to determine the derived discriminant function's statistical significance. A confusion matrix is further used to determine the function's predictive accuracy, whereas the cross-validated predictive accuracy is estimated via the "leave-one-out" classification process.[19]

Linear DFA with a binary (categorical) dependent variable represents the simplest form of DFA in which a single discriminant function is derived. In terms of classification accuracy and predictor extraction, it is similar with binary logistic regression, particularly in sufficiently large populations (ie, >50).[20] In lieu of its capability to produce a predictive linear function that can categorize sizeable populations with considerable accuracy compared with other methods, linear DFA represents a viable approach to our study's aims.

Input Variable Selection for DFA. Input variable selection in linear DFA has been shown to produce

simpler models with improved predictive accuracy that would otherwise be hindered by the presence of redundant variables.[21] In this study, we opted to base the variable selection process by producing a cutoff in the univariate analyses test statistic, ie, the independent samples *t* test.

Comparisons of *t* statistics to a critical value rely mainly on (1) degrees of freedom for a given sample, and (2) the desired (two-tailed) level of significance. If $t_{stat}>t_{critical}$, the null hypothesis of equal group means is rejected.[22] In order to obtain a t_{stat} cutoff, we first determined the average *P* value for all statistically significant variables from the independent samples *t* test (Table II). The values produced a mean of 0.00297±0.00714. For 1226 degrees of freedom, this probability level corresponds to a t_{crit}=2.976. As no $t_{stat} \in [2.976, 3.0]$, the cutoff was rounded to 3.

As spirometry data were available for approximately 938 of 1227 patients, we did not include these variables in the multivariate analysis since it would greatly reduce the predictive power of the discriminant function. Furthermore, spirometry data were based on information from the individual medical history of the patients and not collected by standard procedures, ie, as part of our study or from a single pulmonary clinic. For these reasons, they were included in the univariate analyses as descriptive between groups but otherwise excluded from the multivariate analyses.

By employing a *t* statistic cutoff value ≥3, we selected age, body mass index (BMI), CCI, daytime mean SaO_2, mean SaO_2 during respiratory events, mean saturation during REM (REM mean SaO_2), desaturation index (DI), AHI, number of hypopneas per hour of total sleep time (hypopneas/h), and Epworth Sleepiness Scale (ESS) for the discriminant model.

Subsequently, we retrospectively compared the predictive accuracy of a discriminant function (D_a) including all statistically significant univariate predictors vs a postvariable selection discriminant function (D_b) to determine the optimal model; D_a's predictive accuracy was estimated to be 70.1% vs 73.9% for D_b.

Interpretation of Discriminant Loadings. Discriminant loadings are essentially coefficients describing the correlation between each independent variable and the discriminant function.[19] In a similar manner to typical correlation coefficients (Pearson's or Spearman's), a ±0.30 cutoff is commonly interpreted as the limit between less important and more important variables.[19,23,24] It should be stressed that this interpretation regards the contribution of each predictor to the function; as such, they are qualitatively characterized by their loadings but are not censored from the function itself.

For all analyses, a *P* value <.05 was considered statistically significant. Statistical analysis was performed using SPSS 19.0 (IBM Corporation, San Diego, CA).

RESULTS

Table I shows anthropometric, clinical history, and respiratory characteristics (spirometry and PSG data) of the studied population. Of the studied population, 60.2% had an AHI >15. A total of 554 patients (37.6%) had hypertension, and 392 (70.8%) of hypertensive individuals had an AHI >15.

Anthropometric, clinical history, and respiratory characteristics (continuous variables) of hypertensive and normotensive individuals are presented in Table II. Hypertensive patients were older (mean, 57.1±11.2 years vs 45.8±15.8 years) and more obese (mean BMI, 33.3±6.3 kg/m^2 vs 30.3±5.8 kg/m^2) than normotensive patients.

Univariate analysis determined age, BMI, CCI, ESS, forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, daytime mean SaO_2, mean SaO_2 during respiratory events, minimum SaO_2 during sleep, mean saturation during REM (REM mean SaO_2), DI, AHI, and ESS to be significantly associated with hypertension (Table II). There were no significant differences between hypertensive and normotensive patients in terms of sex and smoking.

Multivariate analysis was subsequently performed via the application of a linear discriminant model. Table III shows the canonical discriminant function coefficients,

TABLE I. Demographic, Respiratory, and Sleep Apnea Characteristics of the Studied Population

Age, y	50±15.3
Male sex %	83.6
BMI, kg/m^2	31.5±6.2
CCI	1±1.6
ESS	9.1±7.2
Current smokers, %	39.5
Hypertensive, %	37.6
FEV_1, %	92.2±34.9
FVC, %	92.7±16.3
FEV_1/FVC	80.7±7.1
Daytime SaO_2, %	97.1±1.8
Mean SaO_2, %	88.7±5.5
Minimum SaO_2, %	78.2±11.6
REM mean SaO_2, %	91.4±6.1
NREM mean SaO_2, %	93.1±23.4
DI	35.7±31
AHI	32±28.2
AI	36.8±28.9

Abbreviations: AHI, apnea-hypopnea index; AI, arousal index; BMI, body mass index; CCI, Charlson Comorbidity Index; daytime SaO_2, daytime mean oxygen saturation; DI, desaturation index; ESS, Epworth Sleepiness Scale; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mean SaO_2, mean oxygen saturation during respiratory events; minimum SaO_2, minimum oxygen saturation during sleep; NREM mean SaO_2, mean oxygen saturation during non-rapid eye movement sleep; REM mean SaO_2, mean oxygen saturation during rapid eye movement. Continuous variables are presented as mean±standard deviation and discrete variables as percentages.

TABLE II. Univariate Analysis Between Hypertension and Demographic, Respiratory, and Sleep Apnea Characteristics

	Hypertensive Patients	Normotensive Patients	Hypertension *P* Value
Age, y	57.2±11.2	45.8±15.8	<.0001
BMI, kg/m^2	33.3±6.3	30.3±5.8	<.0001
CCI	1.8±2	0.5±1.1	<.0001
ESS	10.1±9.9	8.5±4.9	<.0001
FEV_1, %	86.3±18.5	95.9±41.5	<.0001
FVC, %	87.1±16.6	96.3±15.1	<.0001
FEV_1/FVC	79.9±8.3	81.2±6.2	.003
Daytime SaO_2, %	96.6±2	97.5±1.6	<.0001
Mean SaO_2, %	87.7±5.5	89.2±5.3	<.0001
Minimum SaO_2, %	75.5±11.8	80.2±11.1	<.0001
REM mean SaO_2, %	89.8±5.7	92.3±6.2	<.0001
NREM mean SaO_2, %	93.3±39.8	93±3.1	.848
DI	42±29.3	32.1±31.5	<.0001
AHI	36.5±26.6	28.7±28.6	<.0001
Apneas/h	14.4±18	12.2±18.5	.023
Hypopneas/h	22.3±17.9	17.3±17.3	<.0001
AI	39.7±36.2	35.4±24.4	.019

Abbreviations: AHI, apnea-hypopnea index; AI, arousal index; apneas/h, number of apneas per hour of total sleep time; BMI, body mass index; CCI, Charlson Comorbidity Index; daytime SaO_2, daytime mean oxygen saturation; DI, desaturation index; ESS, Epworth Sleepiness Scale; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; hypopneas/h, number of hypopneas per hour of total sleep time; mean SaO_2, mean oxygen saturation during respiratory events; minimum SaO_2, minimum oxygen saturation during sleep; NREM mean SaO_2, mean oxygen saturation during non-rapid eye movement sleep, REM mean SaO_2, mean saturation during rapid eye movement sleep. Values are expressed as mean±standard deviation. Spirometry data were available for approximately 938 of 1227 patients and analyzed with independent samples *t* test.

ie, the unstandardized coefficients used to create the discriminant model:

$$\begin{aligned} D_{(\text{hypertensive vs normotensive})} = {} & 5.132 - 0.025 * \text{MinSaO}_2 \\ & - 0.071 * \text{DaytimeSaO}_2 \\ & + 0.012 * \text{REM meanSaO}_2 \\ & + 0.330 * \text{CCI} + 0.068 * \text{BMI} \\ & - 0.005 * \text{DI} - 0.004 * \text{AHI} \\ & + 0.039 * \text{Age} + 0.005 \\ & * (\text{Hypopneas/h}) + 0.016 \\ & * \text{ESS} \end{aligned} \quad (1)$$

Table IV displays the structure matrix equation (1), namely the correlations between each variable and the discriminant function. By setting a cutoff of 0.3 (absolute value) for the interpretation of the discriminant loadings, age, BMI, CCI, daytime SaO_2, mean SaO_2, minimum SaO_2, and REM mean SaO_2 were deemed as the most accurate predictors for hypertension. AHI, DI, and ESS were not assessed as the most dominant predictive factors for development of hypertension. The overall cross-validated model accuracy of this model was determined to be 73. The single derived discriminant function was statistically significant (Wilk's lambda=0.771, χ^2=289.070, *P*<.0001).

TABLE III. Discriminant Function Coefficients

Variable	Coefficient
Age	0.038
CCI	0.330
BMI	0.068
Daytime SaO_2	−0.071
Minimum SaO_2	−0.025
REM mean SaO_2	0.012
Mean SaO_2	−0.018
DI	−0.005
Hyponeas/h	0.005
AHI	−0.004
ESS	0.016

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CCI, Charlson Comorbidity Index; daytime SaO_2, daytime mean oxygen saturation; DI, desaturation index; ESS, Epworth Sleepiness Scale; hypopneas/h, number of hypopneas per hour of total sleep time; mean SaO_2, mean oxygen saturation during respiratory events; minimum SaO_2, minimum oxygen saturation during sleep; REM mean SaO_2, mean saturation during rapid eye movement sleep.

DISCUSSION

Analysis of our data indicated several statistically significant differences between individuals with hyper-

TABLE IV. Structure Matrix Displaying the Correlation of Each Predictor With the Discriminant Function

Predictors of Hypertension	Discriminant Loadings
Age	0.692
CCI	0.667
BMI	0.446
Daytime SaO_2	−0.426
Minimum SaO_2	−0.386
REM mean SaO_2	−0.350
Mean SaO_2	−0.326
DI	0.284
Hyponeas/h	0.275
AHI	0.243
ESS	0.241
Wilk's lambda=0.771, χ^2=289.070, P<.0001	

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CCI, Charlson Comorbidity Index; daytime SaO_2, daytime mean oxygen saturation; DI, desaturation index; ESS, Epworth Sleepiness Scale; hypopneas/h, number of hypopneas per hour of total sleep time; mean SaO_2, mean oxygen saturation during respiratory events; minimum SaO_2, minimum oxygen saturation during sleep; REM mean SaO_2, mean saturation during rapid eye movement sleep.

tension and those without hypertension. However, age, BMI, comorbidity (CCI), daytime SaO_2, and indices of hypoxia during sleep were estimated to be the most precise predictors for hypertension. In contrast, AHI and DI participated weakly in the statistical model. Therefore, although AHI and DI were independent predictive factors for hypertension, both were not included in the most accurate predictors for development of hypertension. Our findings support that daytime and nocturnal hypoxia play an essential role in OSA-related hypertension.

Scientific data and clinical knowledge about the interaction between OSA and hypertension are continuously increasing. However, whether OSA is truly an independent risk factor for hypertension has yet to be definitively established. The Wisconsin Sleep Cohort revealed a statistically significant association between moderate or worse OSA (AHI ≥15) at baseline and incident hypertension in 4 years (odds ratio of 2.89) compared with those without OSA.[11] In contrast, in the more recent 5-year follow-up from the Sleep Heart Health Study, O'Connor and colleagues[13] reported that the unadjusted risk for hypertension increased in concert with AHI, but that this interaction was not significant after adjustment for BMI. In 2011, Cano-Pumarega and colleagues[14] published data from the Vitoria Sleep Cohort and found that the risk of hypertension increased significantly with higher respiratory disturbance indices, but the odds ratios were no longer significant once adjusted for age and other potential confounding variables. On the other hand, a recent study from Spain identified an increased hazard ratio for incident hypertension in OSA patients compared with control patients, and the correlation between OSA and hypertension remained independent of confounders including age and obesity. Furthermore, follow-up of this patient cohort disclosed a dose-response relationship between the severity of OSA and the cumulative incidence of hypertension.[12]

These discordant conclusions may be related to differences in the study design and the characteristics of the studied populations. Moreover, there are multiple confounding variables for hypertension that usually coexist in OSA patients, such as age and obesity. The prevalence of OSA has been illustrated to increase with age in adults, up to the age of 65.[3,25] In a subgroup analysis of the Sleep Heart Health Study that categorized patients across age groups, OSA patients younger than 60 years were more likely to demonstrate a significant association between minimum SaO_2 and the development of hypertension.[26] Furthermore, it has long been observed that obesity plays an essential role in the development of OSA. It is estimated that 60% to 90% of patients with OSAS are obese.[27] It has recently been proposed that adipose tissue hypoxia may be a trigger of inflammation in obesity, and inflammation is a well-known intermediary mechanism in cardiometabolic dysfunction.[28,29] Thus, our results amplify the current awareness that hypertension and OSA share common risk factors including age and BMI. Our study supports that AHI, DI, and other parameters of SaO_2 included in in-laboratory PSG—expressions of the severity of OSA—are significant determinants of hypertension. Table III shows the correlation of each predictor in the model with the discriminant function. Age, comorbidity (CCI), BMI, daytime SaO_2, and indices of hypoxia during sleep are the most precise predictive factors for hypertension. Nevertheless, AHI participates weakly in the statistical model. It seems that AHI plays a synergistic role with age, comorbidity, obesity, daytime, and nocturnal hypoxia in the development of hypertension.

Moreover, the mechanisms underlying hypertension in patients with OSAS are still incompletely understood. Respiratory events in patients with OSAS and intrathoracic pressure swings cause intermittent hypoxia, recurrent hypercapnia, arousals, and sleep fragmentation, with acute changes in blood pressure and heart rate. Repetitive hypoxia–re-oxygenation plays a pivotal role in the cardiovascular disease process[15–17] and probably activates a broad spectrum of intermediate mechanisms including sympathetic nervous system overactivity,[30,31] inflammation,[32,33] oxidative stress,[34–36] endothelial dysfunction[37,38] and metabolic deregulation involving insulin resistance,[39,40] and disordered lipid metabolism.[41,42] There is increasing evidence that nocturnal hypoxia in OSA patients is associated with the eventual development of daytime hypoxia. Analyzing data from the Sleep Heart Health Study, Sanders and colleagues[43] reported that patients with sleep apnea without obstructive airway disease had a 20-fold higher odds ratio for nocturnal desaturation than that of healthy persons,

even after adjustment for age, sex, height, weight, race, smoking status, and awaking oxygen saturation. A recent study revealed that patients with OSA, in the absence of lung comorbidity, had lower values of daytime partial pressure of oxygen in arterial blood (PaO_2) than those expected on the basis of age. An increase of percent sleep time with reduced SaO_2 was associated with a decrease in daytime PaO_2.[44] Data from the European Sleep Apnea Database (ESADA) cohort study recently showed that both AHI and DI were independently related to prevalent hypertension after adjustment for relevant covariates such as smoking, obesity, dyslipidemia, and diabetes. However, in multiple regression analysis with both DI and AHI in the model, DI was independently associated with prevalent hypertension, whereas AHI was not.[45] In addition to that evidence, we found that daytime mean SaO_2, mean saturation during respiratory events, minimum saturation during sleep, and mean saturation during REM were included in the most accurate predictors for hypertension, whereas AHI and DI were not. It seems that AHI and DI are more complex measures reflecting the degree of intermittent hypoxia, and therefore are susceptible to variability in the clinical setting. We suggest that daytime and nocturnal hypoxemia as consequences of chronic intermittent hypoxia play a central role in OSA-related hypertension. In particular, the shift from chronic intermittent hypoxia to daytime and nocturnal hypoxia may represent a direct prelude to the development of hypertension.

STRENGTHS AND LIMITATIONS

The present data are derived from a large retrospective cohort of patients (1501 individuals) with clinical features of OSAS. All patients underwent full standard in-laboratory PSG. Multivariate analysis was performed via discriminant function analysis. Discriminant analysis produces a linear function of continuous predictor variables that best allocate patients between two or more naturally occurring groups. In the present study, we used discriminant function analysis to determine which continuous variables distinguish between normotensive and hypertensive individuals.

A possible limitation of our study is the choice of the studied population that may not be representative of the general population. We studied individuals who complained of snoring or/and sleep interruption and excessive daytime sleepiness and had been consecutively referred to our laboratory for investigation of possible OSA. However, this should not be a significant limitation since the principal objective was to examine the relationship between OSAS and hypertension. The fact that the majority of the studied population was male may also be a bias of our study. Nevertheless, there are several studies in which the majority of examined patients were men.[12,37,38,45] Furthermore, hypertensive individuals were defined as patients who were previously diagnosed as hypertensive and were also taking at least one antihypertensive agent. Blood pressure measurements taken in the sleep clinic were not used to diagnose hypertension, as these were single readings obtained in the sitting position, which cannot be used as a reliable indicator for a hypertension definition. Moreover, single clinic blood pressure readings might be affected by ongoing medication and could be transiently elevated in some patients because of a white-coat effect.[46,47]

CONCLUSIONS

Our findings amplify the current awareness that there is a significant association between OSA and hypertension. Several well-known risk factors for OSA such as age and obesity are also risk factors for hypertension. Our study revealed that age, BMI, comorbidity, and daytime and nocturnal hypoxia are the most accurate predictive factors for development of hypertension. We suggest that hypoxemia plays an important role in OSAS-related hypertension. Consequently, daytime SaO_2 and indices of hypoxia during sleep should be further evaluated as possible severity markers in OSAS patients.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Predictive level of daytime/nocturnal mean oxygen saturation.

Figure S1. Receiver operating characteristic curve for the discriminant score produced by function (1).

Figure S2. Linear representation of the relationship between the cutoff value and each respective centroid (hypertensive vs normotensive).