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Original research article

Improved prediction of CPAP failure using T90, age and gender

David Slouka [1*], Monika Honnerova [2], Petr Hosek [3], Bretislav Gal [4], Ondrej Trcka [1], Tomas Kostlivy [1], Jana Landsmanova [5], David Havel [2], Martina Baneckova [6], Radek Kucera [7]

[1] *Charles University, Faculty of Medicine in Pilsen, Ear, Nose and Throat Department, Pilsen, Czech Republic*
[2] *Charles University, Faculty of Medicine in Pilsen, Department of Pneumology, Pilsen, Czech Republic*
[3] *Charles University, Faculty of Medicine in Pilsen, Biomedical Center, Pilsen, Czech Republic*
[4] *Masaryk University, Faculty of Medicine, Ear, Nose and Throat Department, Brno, Czech Republic*
[5] *Charles University, Faculty of Medicine in Pilsen, Department of Obstetrics and Gynaecology, Pilsen, Czech Republic*
[6] *Charles University, Faculty of Medicine in Pilsen, Department of Pathology, Pilsen, Czech Republic*
[7] *Charles University, Faculty of Medicine in Pilsen, Department of Nuclear Medicine Laboratory of Immunoanalysis, Pilsen, Czech Republic*

Abstract
Sleep apnea syndrome is associated with increased risk of cardiovascular disease. In treating older patients, there is a special emphasis put on minimally invasive and conservative procedures and a simple method for predicting the potential for treatment success is essential. Continuous positive airway pressure (CPAP) is the first choice for treatment, however, it is not always successful. In cases where CPAP was unsuccessful, treatment with bilevel positive airway pressure (BiPAP) is the next treatment option. In this study, we examine commonly evaluated respiratory parameters, obesity, and age relative to their ability to predict CPAP failure. We also tried to find differences in the predictive ability of these parameters in older and younger patients. The predictive ability, relative to CPAP failure, was examined for each individual parameter as well as for combinations of parameters. All variables had a statistical association with CPAP failure; failure prediction reliability ranged from poor to moderate. Combining T90, age, and gender can be used to find patients who will benefit from BiPAP as the first choice for treatment. An initial BiPAP indication can produce relevant reductions in treatment cost.

Keywords: Age; CPAP failure; Obesity; Prediction of failure; Sleep apnea syndrome

Introduction

Sleep-disordered breathing affects approximately 15% of the population (Mannarino et al., 2012). According to epidemiological studies, more than half of such cases are sleep apnea syndrome (SAS), which affects approximately 2% of middle-aged women and 4% of middle-aged men.

Sleep breathing disorders in the elderly can be accompanied by severe cardiovascular complications (Monahan and Redline, 2011). SAS may cause arterial hypertension (Ture-to-Borges et al., 2018); the presence of apneic episodes disrupts the physiological decrease in systolic and diastolic blood pressure (non-dipper) that normally occurs during night-time sleep. Sleep apnea syndrome is also a risk factor for adverse cardiovascular events such as myocardial infarction, heart failure, and stroke, all of which occur more frequently in SAS patients (Barbé et al., 2012; Kasai, 2012). In patients with untreated SAS, atrial fibrillation is more common and reoccurs more frequently even after successful cardioversion. Similarly, in diabetic patients, glycemic control can be more difficult to achieve without SAS treatment due to changes leading to insulin resistance. Central nervous system symptoms, with excessive daytime sleepiness being the main clinical symptom (Dostálová et al., 2012; Tóthová et al., 2015), severely limit everyday life activities and, in some cases, leads to disability. In older SAS patients especially, associated memory problems and depression can further worsen the quality of life (Bruin and Bagnato, 2010; Onen and Onen, 2010).

Etiologically, there are three forms of SAS: obstructive (OSAS), central, and mixed SAS of different severity. According to the apnea-hypopnea index (AHI) SAS can be classified as AHI 0–4.9, without SAS, AHI 5–14.9, mild SAS, AHI 15–29.9, moderate SAS, and AHI ≥ 30, severe SAS (Butner et al., 2013; Epstein et al., 2009). With increasing age, the proportion of the obstructive form of SAS (OSAS) increases, accounting for up to 80% of senior SAS cases. Central and mixed forms of SAS represent about 10% each (Monahan and Redline, 2011). The first steps in the SAS diagnostic process include sleep monitoring in the Somnology Department and an ear-nose-throat examination (ENT) of the upper respiratory tract. Then, if necessary, specialists from internal medicine, psychology, and stomatology are asked to participate in the diagnosis and/or treatment (Vozoris, 2012).

For patients with moderate to severe SAS, positive airway pressure (PAP) therapy is primarily indicated. The first treatment choice is a single-level device with continuous positive airway pressure CPAP (Chowdury et al., 2012). It is applied through the nose or a full face mask (Williams et al., 2013). Before treatment, it is necessary to carefully choose the mask and determine the correct therapeutic pressure needed to prevent all adverse breathing events (Leidag et al., 2008). If CPAP is unsuccessful, bi-level positive airway pressure (BiPAP) is the next treatment step. Surgical treatment is an option depending on situations where the effect of PAP is limited by the upper airway obstruction (Ephros et al., 2010; Maurer, 2010) or when conservative therapy for severe OSAS has failed (Browaldh et al., 2009; Jalbert et al., 2012).

For older patients, CPAP treatment can initially be technically complicated and difficult to understand. Even a small leak around the nose or full face mask can cause bad function and CPAP failure (Leidag et al., 2008).

Approximately 13% of patients with OSAS experience CPAP treatment failure (Mulgrew et al., 2010; Schäfer et al., 1998). In these patients, CPAP prevents apneic episodes but does not resolve the problem of hypoventilation. Residual AHI values may be normal, but hyposaturation persists. The risk of hyposaturation (hypoventilation) may be particularly high in older OSAS patients. To date, there are no studies that compared the success rates of PAP-treatment in older and younger patients with OSAS and few studies that evaluated factors capable of predicting successful CPAP treatment (Schäfer et al., 1998; Sopkova et al., 2009).

The aim of our study was to compare selected characteristics of SAS in two groups of patients: younger adults (<64.9 years) and older patients (>65 years). Additionally, we wanted to differentiate patients most likely to benefit from CPAP treatment from those who needed BiPAP as the initial treatment (Dohi et al., 2008; Piper et al., 2008).

Materials and methods

Materials
From 2005–2015 a total of 1,253 patients were treated for SAS at the University Hospital in Pilsen, Czech Republic. The study sample consisted of 665 consecutive patients (478 males (72%) and 187 females (28%) with a mean age of 59.1 ± 9.7 years) who met the inclusion criteria (Table 1). A retrospective analysis of the patient's data was carried out. The Ethics Committee of the University Hospital in Pilsen granted approval for data analyses.

Methods
This work was a single center, retrospective cohort study on a sample of patients treated for OSAS using CPAP. Commonly measured respiration parameters from sleep monitoring were compared between successfully and unsuccessfully treated patients. Additionally, the differences in respiration parameters and CPAP success rate between the older and of younger patients (i.e., above and below 65 years, respectively) were evaluated. Lastly, the ability of age and respiration parameters to predict CPAP failure was evaluated both individually and in a multivariate model.

The following variables were recorded and analysed:

- *The BMI (body mass index)* was defined as body weight divided by the square of height; a measure of the degree of obesity.
- *The AHI (apnea-hypopnea index)* was defined as the average number of apnea and hypopnea episodes per one hour of sleep.
- *The ODI (oxygen distress index)* was defined as the average desaturation during sleep.
- *Average saturation* was defined as the mean SaO2 during sleep.
- *The T90* was defined by the percentage of sleep time below 90% SaO2.
- *Treatment failure* was defined as: (A) AHI > 10 and lower than 75% decrease in baseline AHI value and (B) AHI < 10 but persisting hyposaturation, T90 ≥ 10% and ODI ≥ 10. The effect of CPAP was assessed after 3 months of treatment.
- *Inclusion criteria:* (1) OSAS evaluation (diagnosis and follow-up) by the same polygraphic monitoring systems (Miniscreen 8, PolyMesam, Vitaloc, Stardust), (2) the first choice for therapy was a CPAP device, and (3) good compliance with therapy.
- *Exclusion criteria:* (1) previous conservative and/or surgical treatment of OSAS, (2) chronic obstructive pulmonary disease (COPD), (3) alcohol abuse, and (4) incompletely measured data.

Statistical methods
Basic statistics
Associations between CPAP failure and patient age category or gender were tested using the chi-squared test. Because of significantly non-normal distributions for most of the quantitative variables, non-parametric tests were used for subsequent analyses. Respiration parameters were compared between successfully and unsuccessfully treated patients, between genders, and between age categories using the Mann–Whitney *U* test. Mutual correlations between quantitative variables were analysed using the Spearman's correlation coefficient. All reported p-values are two-tailed, and the level of statistical significance was set at $\alpha = 0.05$.

Predictive capability of individual variables
First, the ability to predict CPAP failure from patient age category (with the empirical threshold of 65 years of age) was investigated by calculating the sensitivity and specificity for such stratification. Second, the potential of respiration parameters and age (on a continuous scale) to predict CPAP failure was assessed using the Receiver Operating Characteristic (ROC). An ROC curve was plotted for each variable and the area under the curve (AUC ROC) was then calculated to summarize the predictive strength of the variable as a single value (AUC ROC of 1 representing perfectly reliable prediction and AUC ROC of 0.5 representing random guessing). Sensitivity and specificity were determined for specific threshold values. Confidence intervals for relative frequency, sensitivity, and specificity were calculated according to Agresti and Coull (1998).

Table 1. Characteristics of the studied sample

	Total count	Male	Female	Successful CPAP	Unsuccessful CPAP
All treated patients	1253				
Included in study	665	478	187	575	90
Seniors	158	113	45	125	33
Younger	507	365	142	450	57

Multivariate prediction model of CPAP failure
Based on the best-performing predictors from the single-variable analysis (T90), several multivariate models were constructed using a combination of T90 with other variables not correlated with it, e.g., BMI and age (individually). Both versions of the model (T90 + BMI and T90 + age) were then extended by including gender. The model defined a new predictive variable as a linear combination of the elementary continuous variables. This variable was then assessed in the same way as the single predictors, i.e., using the ROC analysis of a simple threshold-based stratification. For each version of the model, the linear combination coefficients were optimized to maximize the AUC ROC. The optimization was carried out using an enumerative exploration of the whole possible range of rotation angles of the combined factor with respect to the coordinate system defined by the original variables. When gender was included, separate pairs of coefficients were optimized for men and women and then combined into one model.

Basic statistical analysis was performed using STATISTICA (StatSoft, Inc. 2013, Version 12); the ROC analysis and optimization were carried out using MATLAB (Release 2014b, The MathWorks).

Theory
In our work, we focused to find patients with CPAP failure. These patients will benefit from BiPAP as the first choice for treatment. At the time, CPAP is the first choice for treatment, however, it is not always successful. In cases where CPAP was unsuccessful, treatment with BiPAP is the next treatment option. We examine commonly evaluated respiratory parameters, obesity, and age relative to their ability to predict CPAP failure (each individual parameter as well as combinations of parameters).

Fig. 1. Differences in the monitored variables between successfully and unsuccessfully treated patients
Note: (**a**) age; (**b**) AHI; (**c**) BMI; (**d**) T90; (**e**) ODI; (**f**) average saturation.

Results

Analyses of the monitored variables and their relationship to CPAP failure
Of the 665 patients included in the study, CPAP failure was observed in 90 cases (13.5%; 95% confidence interval of CPAP failure rate 11.1–16.4%). All recorded pre-treatment parameters differed significantly between successfully and unsuccessfully treated patients (Fig. 1). All respiration parameters, i.e., AHI ($p = 0.0002$), T90 ($p < 0.0001$), ODI ($p < 0.0001$), and average saturation ($p < 0.0001$) showed more serious breathing insufficiency in patients in whom CPAP failed. Similarly, CPAP failure was significantly associated with higher age ($p = 0.0014$) and BMI ($p = 0.0092$).

When comparing the monitored parameters between age categories (Fig. 2a, b), older patients (>65 years) had a significantly lower AHI ($p = 0.0044$) and ODI ($p = 0.0038$) compared to younger patients, while no differences were observed relative to BMI, T90, and average saturation. The same association was also confirmed on a continuum, in which age was mildly, yet significantly correlated with AHI and ODI (Table 2). The correlation analysis also showed that all the respiration-related parameters, i.e., AHI, ODI, T90, and average saturation, are significantly correlated with one another. Notably, none of the analysed variables were correlated with BMI. Concerning gender (Fig. 2c, d), male patients were significantly younger ($p = 0.0002$) and had higher T90s (0.0152) than females. The remaining patient characteristics, as well as the CPAP failure rate, did not differ significantly between genders.
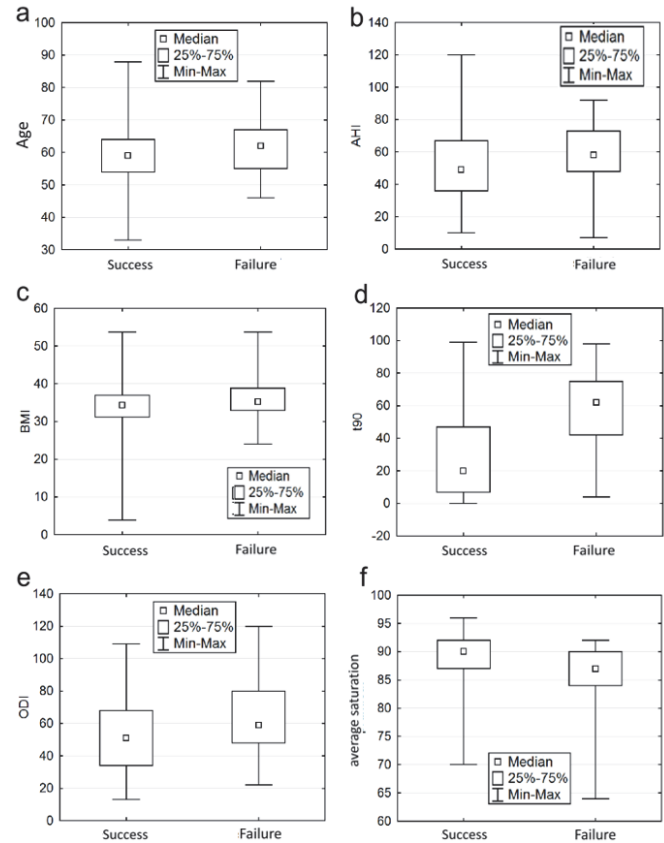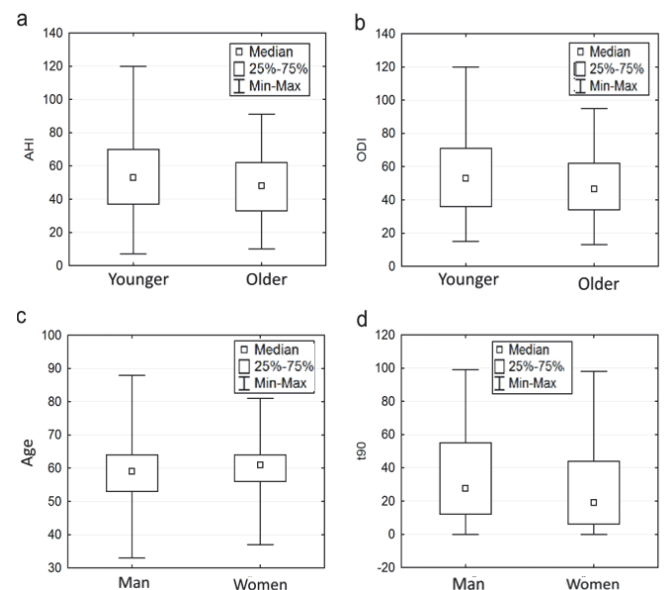

Fig. 2. Differences in the monitored variables between age categories and genders
Note: AHI (**a**) and ODI (**b**) were lower in older patients. Younger age (**c**) and greater T90 (**d**) was observed in men in comparison to women.

Table 2. Correlations between monitored variables. Values of Spearman's correlation coefficient are shown, significant correlations are highlighted and marked in bold typeface.

	Age	BMI	AHI	T90	ODI	Avg. sat.
Age		0.059	**−0.200**	0.011	**−0.229**	−0.021
BMI	0.059		0.049	0.033	0.023	−0.049
AHI	**−0.200**	0.049		**0.530**	**0.763**	**−0.456**
T90	0.011	0.033	**0.530**		**0.645**	**−0.888**
ODI	**−0.229**	0.023	**0.763**	**0.645**		**−0.580**
Avg. sat.	−0.021	−0.049	**−0.456**	**−0.888**	**−0.580**	

Prediction of CPAP failure using individual variables

Following the association between CPAP failure and age demonstrated above (Fig. 1a), significantly higher CPAP failure rates (p = 0.0020) were expectably found in older patients (20.9%; 95% CI 15.1–28.1) in comparison to younger patients (11.2%; 8.7–14.4%). When used as a single predictor of CPAP failure, the older age category showed a sensitivity of 36.7% (27.3–47.2%) and specificity of 78.3 (74.6–81.5%).

Next, the predictive capability of the continuous variables with respect to CPAP failure was investigated using ROC analysis (Fig. 3a–f). The best predictive performance was shown by T90 (AUC ROC 0.791), followed by average saturation (0.723). The remaining parameters performed rather poorly, decreasing in quality from ODI (AUC ROC 0.636), to AHI (0.620), to age (0.605), and lastly to BMI (0.585).

Predicting CPAP failure from multiple variables

While the combined model using T90 and BMI (AUC ROC 0.793) exhibited negligible improvement over T90 alone (0.791), the model combining T90 with age showed a meaningful improvement of prediction quality (0.812, Fig. 3g). Subsequent inclusion of gender brought further improvements to both variants, nonetheless, the model including BMI (i.e., T90 + BMI + gender, AUC ROC 0.801) was still clearly outperformed by the variant featuring age instead (i.e., T90 + age + gender, AUC ROC 0.822, Fig. 3h). The latter was also the best performing predictor constructed from our dataset, reaching almost 80% sensitivity and specificity at their point of equality.

Discussion

Sleep apnea syndrome is a disabling condition that can affect people of all ages but is particularly problematic in older patients, who are more vulnerable to adverse cardiovascular events and disabilities (Monahan and Redline, 2011). Considering that in elderly patients, there is a special emphasis put on minimally invasive and conservative procedures, a simple method for predicting successful treatment is essential.

In our study, we discussed commonly evaluated respiratory parameters, as well as obesity (measured by BMI), and age as predictive factors of CPAP therapy failure. We have tried to find differences in the predictive capabilities of these parameters in elderly and younger patients. To date, this study is, to the best of our knowledge, the largest to explore the interplay between these parameters and CPAP failure.

In our sample, 13% of patients did not achieve satisfactory results after 3 months of CPAP treatment and these patients had to be switched to BiPAP ventilation. Comparable results were published by Schäfer et al. (1998) in a smaller sample of 146 patients. Their findings found BMI and T90 to be predictors. BMI had a median value of 31 in successfully, and 44 in unsuccessfully treated patients, T90 had a median value of 15 in the successfully, and 82 in the unsuccessfully treated group (Schäfer et al., 1998).

Although BMI, AHI, ODI, T90, and SaO2 were statistically significant risk factors for CPAP failure in our work, the ROC analysis suggested that none of these parameters alone can be used for the prediction of CPAP failure with clinically relevant reliability. Their strength as individual variables would have to have been much higher, to reach the limit necessary for clinical significance.

We assumed that age would influence the success rate of CPAP treatment since impairment in cognitive abilities associated with older age would be expected to impact compliance (Šedová et al., 2016). Good communication plays a particularly critical role in elderly patients (La Piana et al., 2011; Morales et al., 2012). Our supposition was confirmed; however, the predictive ability of age was found too weak for clinical praxis. T90 proved to be a predictor of treatment outcomes in line with Schäfer's as well as our previous conclusions based on a smaller sample (Schäfer et al., 1998). When we used combined models we got pronounced increases in the predictive ability, i.e., with the T90 and age combination (AUC ROC 0.812, Fig. 3g) and even better with the T90, age, and gender combination (AUC ROC 0.822, Fig. 3h). Unfortunately, we were not able to compare our conclusions because no other studies have tried using combined models of predictive factors relative to CPAP treatment failure.

We are aware that a single center study may limit the generalization of our results, even though our sample of patients was large and unselected (representative) from a large regional University Hospital. The demographic distribution of our patients supports our findings (Monahan and Redline, 2011), nonetheless, prospective multi-center studies would be useful for continued exploration of the problem.

Conclusions

The number of patients with SAS is significant and as medical care continues to improve, the number of patients diagnosed and treated for SAS can be expected to increase. The medical and socio-economic impact of untreated or poorly treated patients is serious, and as such requires proper diagnosis and treatment. A model that combines T90, age, and gender greatly facilitates finding patients who will benefit from BiPAP as the first-choice device, and therefore, should produce relevant reductions in treatment cost associated with SAS.

Ethical aspects
The Ethics Committee of the University Hospital in Pilsen granted their approval to the data analyses.

Conflict of interests
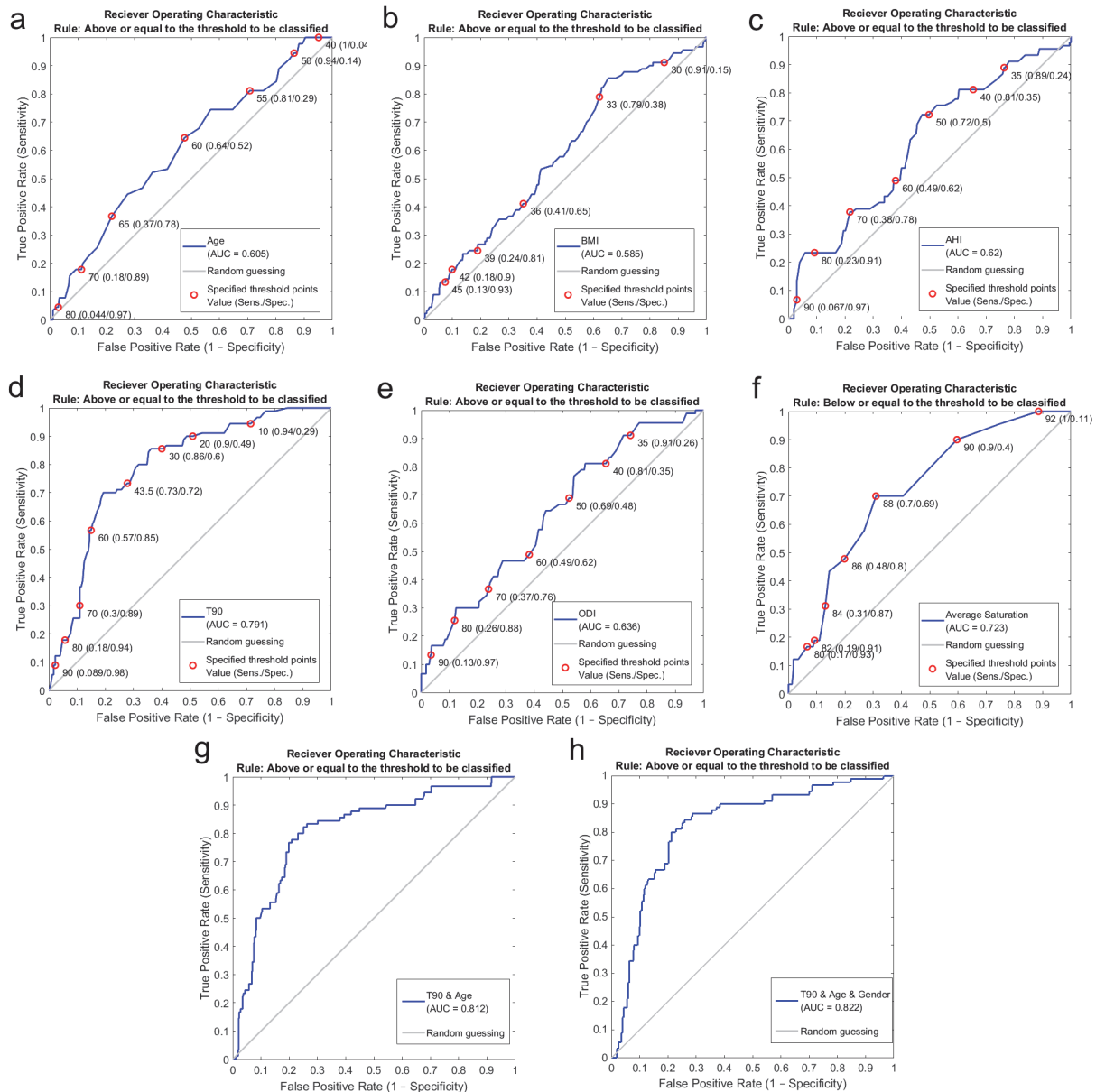The authors have no conflict of interests to declare.

Fig. 3. ROC curves for CPAP failure prediction
Note: (**a**) age; (**b**) BMI;(**c**) AHI; (d) T90; (**e**) ODI; (**f**) average saturation; (**g**) combined model using T90 and age; (**h**) combined model using T90, age, and gender.

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