Original Article

Predictive factors for CPAP failure in obstructive sleep apnea patients

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ABSTRACT

Objectives: Some patients with obstructive sleep apnea (OSA) do not respond to Continuous Positive Airway Pressure (CPAP) and for these patients, Bi-level PAP is the next level modality. This study by a theory driven hierarchical approach, tries to identify the predictors for CPAP failure among OSA patients. **Methodology:** The potential predictors for the model were identified from a theoretical framework rooted in clinical examination, laboratory parameters, and polysomnographic variables pertaining to OSA patients. All patients of OSA who underwent manual titration with CPAP or Bi-level PAP (in case of CPAP Failure) between June 2015 and October 2017 were included in model building. This study compared five competitive models blocks deliberated by increasing order of diagnostic complexity and availability of resources. The fitting of the model was determined by both internal and external validation. **Results:** Among the five competitive models, the selected model has the significant deviance reduction (−2LL = 121.99, X^2 = 25.55, P < 0.0001) from the baseline model (−2LL = 217.356). This logistic regression model consists of the following binary predictors – Age >60 years (odds ratio [OR] = 3.23 [1.27–8.23]), body mass index >35 Kg/m^2 (OR = 4.25 [1.78–10.13]), forced expiratory volume <60% (OR = 7.33 [2.83–18.72]), apnea-hypopnea index >75 (OR = 4.31 [1.61–11.56]) and T90 > 30% (OR = 6.67 [2.57–17.36]). **Conclusion:** These five factors (acronym as BIPAP) may aid to the clinical decision-making by predicting failure of CPAP and therefore may assist in more vigilant clinical care.

KEY WORDS: Apneas, Obstructive Sleep, CPAP Ventilation, BiPAP Bilevel Positive Airway Pressure, CPAP, failure

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INTRODUCTION

Obstructive sleep apnea (OSA) is a sleep breathing disorder which creates a mismatch in airflow and efforts put for the same. A steady stream of pressurized air through positive airway pressure (PAP) has been the fundamental principle behind the devices evolved to treat OSA patients. With the advent of technology, many variants of the primary continuous positive airway device (CPAP) have evolved. These variants are rooted in various algorithms generated intuitively to pursue and mimic the physiological air in/out flow at differential severity of disease. Bi-level PAP is such a variant which uses dual pressure setting facilitating augmented in/outflow of air in alignment with respiratory pattern. Bi-level PAP is prescribed when CPAP fails in patients with OSA. Few studies have tried to find factors

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associated with bi-level PAP prescription (i.e., CPAP failure).[1-3]

Thinking from pathophysiological plane and biological intuitive logic, there may be several attributes which in different permutation-combinations may optimize the candidature for CPAP/AutoPAP or Bi-level PAP.[4] To the best of our knowledge, we do not have any evidence till date that is driven clinically to provide meaningful cut-off for predictive variables for Bi-level PAP prescription. The clinical implication of knowing these predictors beforehand may be translated into a more vigilant follow up of those patients who may require bi-level PAP with higher odds by priority triaging them. Thus, the aim of this study is to find out the predictors for failure of CPAP therapy among patients of OSA.

METHODOLOGY

Study setting and population

A retrospective study was done in OSA patients diagnosed in our sleep laboratory from June 2015 to November 2017. All OSA patients who fulfilled all three criteria were enrolled in this study:

1. Age >18 years
2. Diagnostic Polysomnography showed apnea-hypopnea index (AHI) >15
3. Patient underwent PAP manual titration in hospital.

Procedure

All patients underwent level I PSG (Philips Respironics Alice 6). Apneas and Hypopneas were scored according to AASM scoring manual 2012.[5] Patients were titrated with CPAP, if patient had AHI >15. All patients underwent in labortory titration. CPAP pressure was increased by 1 cm H_2O, if there were 2 obstructive apneas or 3 hypopneas or 5 RERA or 5 min of loud snoring. If the patient did not settle with CPAP (till 18 cm H_20) or if the patient found pressure to be uncomfortable, he/she was shifted to bi-level PAP. In bi-level PAP, both Inspiratory PAP and Expiratory PAP were increased by 1 cm H20 (to maintain IPAP-EPAP gap between 4 and 10 cm H20) till all obstructive events were abolished. Then, IPAP was increased by 1 cm H20 for the presence of 3 hypopneas or 5 RERA or 5 min of loud snoring. All patients with OSA could be successfully titrated with either CPAP or Bi-level PAP (in case of CPAP failure).

Each sleep study was manually scored first by RPSGT certified sleep technician and was cross checked by sleep consultant. Severity of OSA was determined by three parameters namely AHI, nadir oxygen levels (minimum oxygen saturation during sleep) and percentage of total time with oxygen saturation level lower than 90% during sleep (T90%). Spirometry was done in all OSA patients in accordance with the current standardization recommendations of the ATS-ERS. Quart pneumotach (X9) spirometer (Cosmed, Italy) was used. Validated prediction equation for north Indians was used for calculating forced expiratory volume (FEV_1), forced volume capacity (FVC), and FEV_1/FVC.[6]

The potential predictors (independent variables) were first converted into categorical variables for making useful predictions from clinical perspective and as an attempt to generate eligibility threshold for validation by future prospective study. Cut-off point for variables was determined by adapting the following procedure:

1. Maximum statistic approach: By dividing the data into deciles and then to apply a two-sample *t*-test on selected sections with the Bonferroni correction
2. Drawing a ROC curve and calculation of Youdens index for achieving the optimum sensitivity and specificity
3. Creating grouped data plots by grouping the continuous covariate into deciles and then plotting the average covariate value within each decile against the proportion undergoing the Bi-level PAP in that decile.

Model building and development

The model in this study was selected through the hierarchical method by a theory driven approach. The hierarchy level for competitive models was determined by resource intensiveness and increasing complexity in making diagnosis (from clinical and anthropological examination alone to Level III polysomnography). The theoretical framework of same is shown in Figure 1.

The competitive models were compared with omnibus tests of model coefficients for detecting the improvement from one model over another. All the variables from the apex model which had a $P < 0.10$ (or clinically relevant) were selected for the final multivariate analysis. These selected variables were checked for multicollinearity by correlation matrix and interactions terms. Then, the analysis was run again with the selected independent variables for goodness of fit (GOF) and regression diagnostics of model. The odds ratio and the confidence intervals for all the independent variables were calculated.

Validation

Model validation

The study determines both internal and external validity of the proposed model. Internal validation was done mainly to find out internal consistency, illogical errors and outliers for which maximum cooks distance, observed leverage values, and residuals were calculated. The

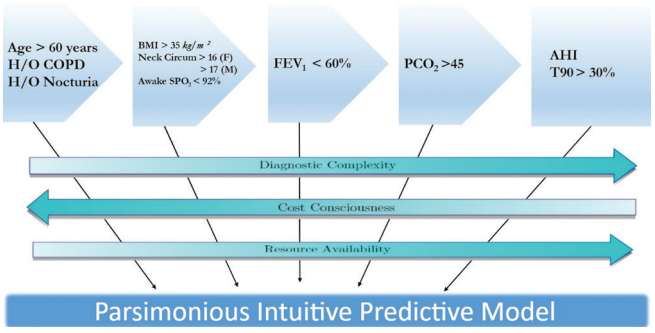

Figure 1: Conceptual framework – Hierarchical blocks as per intricacies in diagnostics and ease of use

Hosmer–Lemeshow statistic was calculated to detect the model fitting to the data.

For external validation, prospective external validation was done with a separate cohort of 45 OSA patients (hold-out method of cross-validation) where predicted values for mode of treatment were compared with actual observed values. A cut-off of 0.5 was used for the model prediction. Further c-statistics was calculated by area under curve (AUC). A confusion matrix was made for detecting misclassification error and extent of agreement between observed and predicted values. The validation was done by the "pROC" package in R statistical software.

Ethical clearance

This study was approved by institutional ethical committee of AIIMS Bhopal. Informed written consent was obtained from every patient.

RESULTS

There were 216 (170 males and 46 females) patients in CPAP group against the 42 patients (24 males and 18 females) in Bi-level PAP group. The mean age of the participants in the CPAP group was 51.31 ± 11.45 years and 55.5 ± 10.38 years for bi-level PAP group. Other relevant baseline anthropo-clinical characteristics of the participants are shown in Table 1.

Table 2 shows the overall model statistics for each of the five competitive models. After the selection of the variables for final model, we iterated the process for model fitting to data. Table 3 shows the beta coefficients (with standard errors) of variables selected for the final model, along with the odds ratios with its confidence intervals. The discrimination plot reporting the predicted probabilities is shown in Figure 2.

Model diagnostics

To summarize the internal validity measures, maximum cook's distance was found to be 0.059 for this model. Observed leverage values lay between 0.05 and 0.03 against the expected value of 0.19. Around 4.7% values of studentized residuals lies outside the ± 1.96 standard deviation. The presence of influential observations (observations having the potential to change the results significantly) were detected through DFBETA values which was found to be <1 (below the threshold cut off. The maximum DFBETA was 0.253 (for constant parameter). Hosmer–Lemeshow GOF test revealed a Chi-square of 6.456 (P = 0.374), suggesting that the model is a good fit.

Results of model diagnostics

The AUC in the ROC curve has the value 0.73 (95% CI: 0.514–0.947) [Figure 3]. The confusion matrix shows the predictive accuracy of model as 77.78% with a misclassification error rate of 22.22%. The agreement between the predicted and observed values was estimated using Cohen's Kappa, which was 0.324 (95% confidence interval [CI]: 0.014–0.635, P = 0.041) [Table 4].

Table 1: Point and interval estimates of participants' anthropo-clinical characteristics grouped by therapy

Characteristics	Mean±SD	
	CPAP group (n=216)	Bilevel PAP group (n=42)
BMI (kg/m^2)	30.27±5.74	36.50±7.21
PCO_2	47.05±22.20	45.93±18.03
HCO_3	33.93±26.84	30.61±19.83
FEV_1	75.30±32.92	52.92±39.05
FVC	70.86±31.19	49.16±34.77
ESS	8.44±4.84	9.43±5.51
Lowest O_2	79.98±12.70	64.29±18.09
SpO_2	95.71±2.40	94.19±3.85
STOPBANG	4.49±1.25	4.95±1.65
AHI	59.72±32.69	87.34±34.48
Neck circumference (cm)	15.87±1.29	16.42±1.75
T90	7.025±13.84	37.79±33.62

PAP: Positive airway pressure, CPAP: Continuous positive airway device, BMI: Body mass index, PCO_2: Partial pressure of carbon dioxide, FVC: Forced volume capacity, FEV_1: Forced expiratory volume in 1 s, ESS: Epworth Sleepiness Scale, O_2: Oxygen, SpO_2: Severity and the degree of oxygen, AHI: Apnea-hypopnea index, SD: Standard deviation

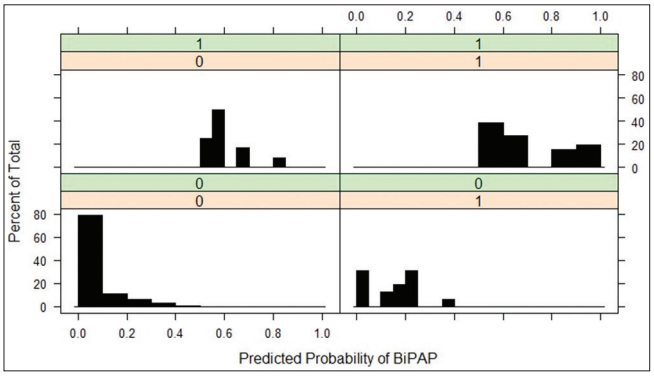

Figure 2: Discrimination matrix showing the predicting ability of the model to correctly classify the participants into continuous positive airway device (0) or Bi-level PAP (1) group. (here probability ≥0.05 denotes the classification in Bi-level PAP group)

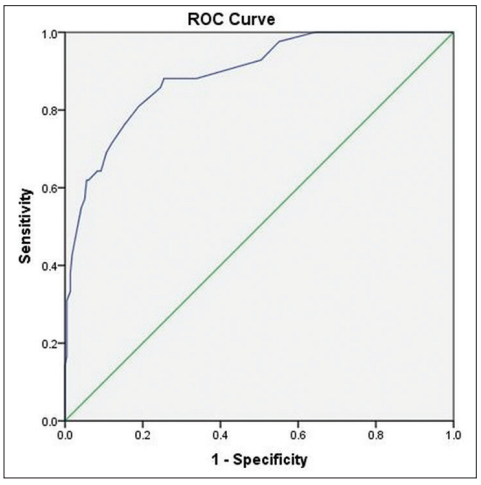

Figure 3: Receiver operator characteristic curve showing the overall predictive accuracy of the model

Table 2: Model statistics and performance of all the all competitive models arranged in a hierarchical diagnostic complexity

Competitive model	Representing variables	Deviance (−2LL)	Omnibus test of model coefficient		Hosmer-Lemeshow test	
		Constant	χ^2	*P*	H-L statistic	*P*
Baseline		217.356				
Model 1	H	194.445	22.911	<0.0001	2.139	0.544
Model 2	H+E	160.321	34.123	<0.0001	4.653	0.702
Model 3	H+E + PFT	147.965	12.356	<0.0001	3.563	0.829
Model 4	H+E + PFT+ABG	147.545	0.42	0.517	5.812	0.688
Model 5	H+E + PFT+ABG+SS	121.993	25.552	<0.0001	3.859	0.870

H: Clinical history, E: Basic evaluation, PFT: Pulmonary function test, ABG: Arterial blood gas, SS: Sleep study, H-L: Hosmer-Lemeshow

Table 3: Odds ratio with confidence interval of variables showing strength of association with bi-level positive airway pressure

Variables	Beta (SE)	Wald statistics (*P*)	OR	95% CI	
				Lower	Upper
Age >60 (years)	1.173 (0.477)	6.053 (0.014)	3.232	1.269	8.229
T90 >30 (%)	1.889 (0.488)	15.153 (0.00)	6.676	2.567	17.365
AHI >75	1.462 (0.503)	8.458 (0.004)	4.315	1.611	11.559
BMI >35 kg/m^2	1.448 (0.443)	10.681 (0.001)	4.253	1.785	10.134
FEV_1<60 (%)	1.992 (0.478)	17.361 (0.000)	7.333	2.873	18.720
Constant	−4.577 (0.591)	59.992 (0.000)	0.010		

Hosmer and Lemeshow 6.456 (P=0.374, df=6), R^2=0.49 (Nagelkerke) model−2LL=141.151, Df=1 for all variables. SE: Standard error, CI: Confidence interval, OR: Odds ratio, AHI: Apnea-hypopnea index, BMI: Body mass index, FEV_1: Forced expiratory volume in 1 s

Table 4: Confusion matrix showing the extent of agreement between model prediction and real world observation

Predicted	Observed		Total
	CPAP	BiPAP	
CPAP	31	4	35
BiPAP	2	8	10
Total	33	12	45

CPAP: Continuous positive airway device, BiPAP: Bi-level positive airway pressure

DISCUSSION

This study has attempted to find predictors for requirement of Bi-level PAP device in OSA patients. From clinical standpoint, if a patient has any of the five characteristics (body mass index [BMI] >35 Kg/m^2; AHI >75; FEV_1 <60%, Age >60 years and Pulse oximetry time below 90% (T90) >30% of total sleep time), then he may have a higher probability to settle with bi-level PAP and not by CPAP. Based on finding of the study, we have devised an acronym for the predictors of CPAP failure: BIPAP which stands for BMI, Index (AHI), PFT (FEV_1), age and pulse oximetry (T90), respectively.

OSA is associated with lot of consequences (metabolic, cardiovascular and neurological) and treatment with PAP has been shown to reduce these complications.[7-11] Previously, some authors have tried to find factors associated with Bi-level PAP prescription. A study from Italy on 105 patients found higher AHI, lower mean SpO_2, FVC and FEV_1, hypercapnia and COPD as factors associated with Bi-level PAP prescription.[1] Few studies have also found T90, higher BMI, older age, pCO_2, AHI, COPD, sleepiness, and nadir O_2 as predictors of CPAP failure.[2,3] All these studies have established a relationship on a continuous scale chiefly. Our study further attempted to translate the association into a clinically meaningful binary cut off; which can help to classify and prioritize OSA patients even by non-sleep physicians. Another strength of this study lies in the fact that majority of the studies conducted for finding association have performed level-III PSG (or HST) and not level-I PSG (Lab-based titration) while in our study we did level-I PSG for all patients.

T90 (%time spent by a patient during sleep with the saturation values <90%) is indicative of severity of oxidative stress due to OSA. T90 >30% was found to have the highest odds (O.R. 6.68) associated with failure of CPAP therapy. This was consistent with earlier studies, where T90 was associated with CPAP failure.[2,3]

The implication of this study may be thought in the following context. When level I PSG titration is done, physician is usually certain about the mode and pressure requirement of the patient. Level-I PSG is resource and labor intensive hence cost implications are more. Because of this fact, HST/level-III PSG is now preferred worldwide. After HST, patient is usually prescribed AutoPAP and asked to visit again after 2–4 weeks with downloaded data. If the patient improves symptomatically and download data also show favorable results, then the patient is either given AutoPAP device or he/she can be given fixed pressure CPAP with pressure of P90/P95 (depending on the manufacturer). If patient does not improve with AutoPAP, he/she is taken for in laboratory polysomnographic titration (level-I) with CPAP followed by bi-level PAP (if required). Patients usually require bi-level PAP when they have failed titration on CPAP or cannot tolerate CPAP at higher pressures.[12]

After doing a diagnostic PSG, if one or more of above-mentioned five factors is positive then physician should be more vigilant accordingly about the possible CPAP failure or the requirement of bi-level PAP. This tool also assigns a decision making capacity to non somnologist up to an extent.

One of the important factors of adherence to any PAP device is the initial experience with that machine.

OSA is associated with lot of consequences (metabolic, cardiovascular and neurological) and treatment with PAP has been shown to reduce these complications.[13,14] This first experience with a "foreign body" determines the overall compliance with PAP therapy. If a patient who requires bi-level PAP is prescribed AutoPAP, then he will not improve and may develop aversion to any PAP and may not use Bi-level PAP when prescribed. In the current study, around 20% of patient failed CPAP titration and ultimately settled with bi-level PAP. The implication of this failure should also be seen from adherence perspective.

In spite of single-center study with limited participants, this study may help in better triage of patients and more efficient use of level I PSG and HST at first glance. However, its utility to streamline patients to Auto-CPAP or Bi-level PAP needs to be seen by future multi-centric studies.

CONCLUSION

This model consisting of five binary factors (acronym as BIPAP) may aid to clinical decision by predicting probability of failure of CPAP and therefore may assist in more vigilant clinical care. It can also help in triaging patients who will require in laboratory titration instead of AutoCPAP prescription.

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Conflicts of interest
There are no conflicts of interest.

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