Original Article

Predictors of obesity hypoventilation syndrome among patients with sleep-disordered breathing in India

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ABSTRACT

Introduction: No study has been done in India to evaluate obesity hypoventilation syndrome (OHS) among patients with sleep-disordered breathing (SDB). The known predictors of OHS, i.e., body mass index (BMI) >35 kg/m^2 and forced vital capacity (FVC) <3.5 L for men and <2.3 L for women from western countries, cannot be applied to Indian patients. **Objectives:** To find out the prevalence of OHS and to determine the predictors of OHS among Indian SDB patients. **Materials and Methods:** It was a retrospective observational study conducted in a tertiary care institute from September 1, 2017, to August 31, 2018. All the patients who underwent polysomnography were analyzed for the presence of OHS. Of 85 patients referred for polysomnography, 76 had SDB. Thirteen patients were excluded because of hypoventilation due to other known causes or could not perform spirometry. **Results:** The prevalence of OHS among SDB after excluding the other causes of hypoventilation was 15.87% (10/63). The predictors were determined using univariate analysis between daytime partial pressure of carbon dioxide ($PaCO_2$) and other predictors. $PaCO_2$ significantly correlated with minimum nocturnal oxygen saturation by pulse oximetry (SpO_2), FVC %predicted, BMI, daytime SpO_2, forced expiratory volume %predicted, and partial pressure of oxygen (PaO_2). Following a stepwise multiple regression, minimum nocturnal SpO_2, FVC %predicted, and BMI were found to be independent predictors of OHS. A minimum nocturnal SpO_2 threshold of 60%, FVC %predicted <74.5%, BMI >30.95 kg/m^2, and absolute FVC <2.33 L for men and <1.68 L for women were found to be predictors of OHS. **Conclusion:** The prevalence of OHS in Indian patients is similar to Caucasians. OHS is seen in Indian patients even at a lower BMI and lower spirometric parameters.

KEY WORDS: Obesity hypoventilation syndrome, predictors, sleep-disordered breathing

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INTRODUCTION

Sleep-disordered breathing (SDB) refers to a group of disorders comprising obstructive sleep apnea (OSA), obesity hypoventilation syndrome (OHS), central sleep apnea, Cheyne–Stokes respiration, and upper airway resistance syndrome. OSA is the most common type of SDB. Central sleep apnea, Cheyne–Stokes respiration, and upper airway resistance can easily be identified on polysomnography whereas the diagnosis of OHS requires additional arterial blood gas (ABG) analysis.[1] Based on various studies from other countries, the prevalence of OHS in the general population varies from 0.15% to 0.4%[2-4] whereas that among patients of SDB is 10%–30%.[5-7] However, till date, there are no studies from India on the prevalence of OHS. OHS is associated with significant morbidity and mortality. OHS patients as compared to

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eucapnic patients of SDB have lower quality of life, greater risk of pulmonary hypertension, cor pulmonale, higher need of mechanical ventilation with longer hospital stay, and more health-care expenses.[8-11] The management of OHS also differs in that OHS often requires bilevel positive airway pressure with or without oxygen.[12]

Performing ABG routinely for the diagnosis of OHS is limited by its invasive nature, skill of the clinician, and access to costly analysis equipment. Identification of simpler clinical predictors of OHS is, thus, helpful in reducing the requirement of ABG in all SDB patients. There are many studies in Caucasian population which have found predictors of OHS. Body mass index (BMI), apnea–hypopnea index (AHI), forced vital capacity (FVC), minimum nocturnal oxygen saturation by pulse oximetry (SpO_2), daytime SpO_2, etc., are some of the predictors established for the Caucasian population. Because the anthropometry and morphological characteristics of Indian patients vary from that of the Caucasian population, those predictors cannot be applied to our patients.

Hence, we performed this study, first of its kind from India to find out the prevalence of OHS and the various predictors of OHS in our SDB patients. The definition and diagnostic criteria of OHS are BMI >30 kg/m^{-2}, daytime partial pressure of carbon dioxide ($PaCO_2$) ≥45 mmHg and AHI ≥5, or sleep hypoventilation. 90% of the cases of OHS have AHI ≥5/h, whereas only 10% have sleep hypoventilation.[1,2,13] Sleep hypoventilation is assessed by nocturnal CO_2 monitoring during polysomnography. Nocturnal CO_2 monitoring is indicated in patients with daytime $PaCO_2$ ≥45 when polysomnography does not show OSA.[13] There is also a new terminology called "obesity-related sleep hypoventilation" (ORSH), wherein the patient has only nocturnal hypoventilation without any daytime hypercapnia. This represents the early stage of hypoventilation in obesity which may eventually progress to OHS.[14] The implication of ORSH on long-term consequences and management are not known.

MATERIALS AND METHODS

It was a retrospective observational study conducted in the Department of Pulmonary Medicine, ESI-PGIMSR, New Delhi, from September 1, 2017, to August 31, 2018, after taking ethics committee approval. Inclusion criteria are as follows: all adults undergoing polysomnography were evaluated for possible inclusion. OHS was diagnosed if following criteria were satisfied: (1) obesity (BMI >30 kg/m^2), (2) daytime hypercapnia ($PaCO_2$ ≥45 mmHg), (3) SDB (AHI ≥5 or sleep hypoventilation), and (4) other known causes of hypoventilation excluded.[1,2,13] Exclusion criteria are as follows: (1) the presence of other causes of hypoventilation such as severe obstructive or restrictive pulmonary diseases, chest wall disease like kyphoscoliosis, neuromuscular disease, diaphragmatic paralysis, severe hypothyroidism, congestive heart failure, or renal failure and (2) failure to perform spirometry.

Our department protocol entailed all the patients undergoing polysomnography to have detailed clinical evaluation, laboratory workup, daytime ABG analysis, spirometry, and chest radiograph to be recorded in a pro forma. The clinical evaluation included demographics, symptoms of SDB (snoring, witnessed apnea, and excessive daytime sleepiness), patient's vital parameters, and anthropometric measurements (BMI, waist circumference, and neck circumference). BMI was calculated using the standard formula: weight (kg)/height^2 (m^2). Neck circumference was measured at the level of the cricothyroid membrane using a measuring tape. Waist circumference was measured at the level of midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the midaxillary line. SpO_2 was measured using daytime pulse oximetry in sitting position. Daytime sleepiness was assessed using the Epworth Sleepiness Score (ESS). STOP-BANG questionnaire was used to calculate the risk of OSA. Laboratory workup included complete metabolic profile including complete blood count, liver function, kidney function, thyroid function tests, lipid profile, and electrocardiogram at rest. Chest radiograph was performed to establish the diagnosis of underlying respiratory disorder. ABG analysis was performed with patient's consent during daytime and on room air after 15 min of rest. Spirometry was performed according to the American Thoracic Society guidelines.[15] Forced expiratory volume in 1st second (FEV_1) and FVC were recorded as absolute values as well as in percentage of predicted.

The full-night attended polysomnography was performed for all the patients on Philips Alice S5 polysomnograph and it included recording of electroencephalogram (central and occipital), electrooculogram, submental and pretibial electromyography, oronasal flow (thermistor and nasal pressure transducer), thoracoabdominal movements, and SpO_2. Sleep stages and respiratory events are scored according to the American Academy of Sleep Medicine guidelines.[16]

Statistical analysis

Analysis was performed using SPSS software version 17 (IBM, SPSS version 17, Chicago). The data were presented as mean ± standard deviation. The prevalence of OHS was determined by establishing proportion of patients meeting criteria for the diagnosis of OHS. The data were compared among patients with OHS and those without OHS using Student's *t*-test, Chi-square test, or Mann–Whitney U-test wherever applicable. Further analyses were conducted to assess the utility of various parameters in predicting hypercapnia using regression analyses. The receiver operating characteristic (ROC) analyses were utilized to find out the cutoff level of various predictors. $P < 0.05$ was considered statistically significant. Sample size was calculated using the standard formula: $n = Z^2_{1-\alpha/2} * P(1-P)/d^2$, where n = number of patients required, Z = confidence interval of 95%, P = anticipated population proportion,

and d = precision required.[17] A minimum sample size of 62 was required with a precision of 0.10.

RESULTS

A total of 85 patients were referred to our center with clinical suspicion of SDB. After undergoing polysomnography, 76 (89.4%) patients were proven to have SDB. None of the patients without SDB had daytime hypercapnia. Further, 12 patients were excluded because of the presence of other causes of hypoventilation. One patient who could not perform spirometry due to the presence of bilateral severe temporomandibular joint ankylosis was also excluded. Hence, final cohort of 63 patients was analyzed for the prevalence of OHS and evaluation of various predictors of OHS. Figure 1 shows the flow diagram of patient inclusion and prevalence of various SDBs in our study.

The study population involved adults ranging from 26 to 70 years with a mean age of 50.42 ± 9.97 years. It consisted of 44 (69.84%) men and 19 (30.16%) women. The mean BMI was 33.13 ± 6.05 kg/m^2. Among the types of SDB, OSA was seen in majority of patients, i.e., 59 (93.65%) patients. Of 63 patients, 26 (41.27%) had severe OSA, 17 (26.98%) had moderate OSA, and 16 (25.4%) had mild OSA. Upper airway resistance syndrome was found in only 4 (6.34%) patients. A total of 10 (15.87%) out of 63 patients fulfilled the criteria of OHS. All the patients of OHS had concurrent OSA. Daytime hypercapnia was not found in any patient with upper airway resistance syndrome. Of the 10 OHS patients, 60% (6 patients) were men and 40% (4 patients) were women. Table 1 shows the prevalence of OHS as per sex distribution, severity of obesity, and severity of OSA. The prevalence of OHS among women was higher as compared to men (21.05% vs. 13.63%). With increasing severity of obesity and OSA, the frequency of OHS also increased.

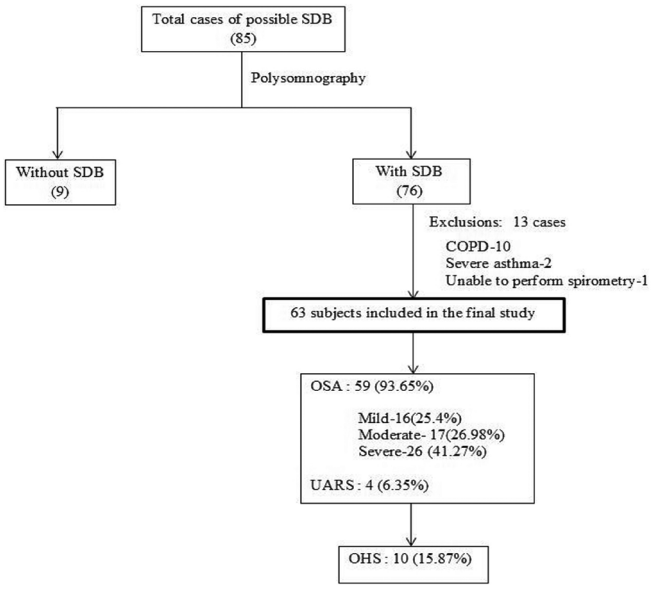

Figure 1: Flow diagram showing the study population after applying inclusion and exclusion criteria and the prevalence of various forms of sleep-disordered breathing

Various parameters such as demographic, anthropometric characteristics, sleep scores, pulmonary functions, and polysomnographic findings were compared among patients with OHS and those without OHS as shown in Table 2. Age and sex distribution in both the groups were comparable with no significant difference. Those with OHS as compared to those without OHS had significantly higher BMI (38.01 ± 6.91 vs. 32.20 ± 5.46, P = 0.004) and poorer

Table 1: Prevalence of obesity hypoventilation syndrome as per various parameters

Parameter	Total number of patients	Number of patients with OHS (prevalence in percentage)
Sex		
Male	44	6 (13.63)
Female	19	4 (21.05)
Severity of obesity, BMI (kg/m^2)		
>30	42	10 (23.8)
>40	8	3 (37.5)
>50	1	1 (100)
Severity of OSA		
Mild	16	1 (6.25)
Moderate	17	2 (11.76)
Severe	26	7 (26.92)

BMI: Body mass index, OHS: Obesity hypoventilation syndrome, OSA: Obstructive sleep apnoea

Table 2: Various characteristics of patients with obesity hypoventilation syndrome compared to those without obesity hypoventilation syndrome

Parameter	With OHS (n=10)	Without OHS (n=53)	P
Demographic parameters			
Age	50.10±11.35	50.49±9.80	0.911
Sex (male:female)	60:40	71.7:28.3	0.472
Anthropometry			
BMI	38.01±6.91	32.20±5.46	0.004
Waist circumference	114.25±14.82	104.49±14.90	0.090
Neck circumference	42.1±3.82	38.92±3.77	0.015
Sleep scores			
ESS	18.8±5.51	15.68±5.55	0.080
STOP-BANG	5.7±1.45	5.15±1.43	0.260
Spirometric parameters			
FEV_1	1.89±0.55	2.02±0.54	0.470
FEV_1% predicted	63.40±9.46	73.06±13.26	0.032
FVC	2.44±0.67	2.61±0.67	0.450
FVC %predicted	66.80±9.126	78.13±13.07	0.011
FEV_1/FVC	79.57±10.26	91.29±84.09	0.664
Other lung functions			
Daytime SpO_2	94.10±3.31	96.15±4.02	0.130
pO_2	66.52±29.75	80.55±23.68	0.105
HCO_3	32.24±4.35	27.49±10.19	0.182
Polysomnography			
AHI	32.31±11.97	30.24±25.02	0.275
Minimum nocturnal SpO_2	50.7±12.6	74.87±16.54	<0.001

AHI: Apnea–hypopnea Index, BMI: Body mass index, ESS: Epworth Sleepiness Score, FEV1: Forced expiratory volume in 1st s, FVC: Forced vital capacity, OHS: Obesity hypoventilation syndrome, OSA: Obstructive sleep apnea, SpO_2: Oxygen saturation by pulse oximetry

lung functions, i.e., FEV_1%predicted (63.40 ± 9.46 vs. 73.06 ± 13.26, $P = 0.032$), FVC %predicted (66.80 ± 9.13 vs. 78.13 ± 13.07, $P = 0.011$), and lower minimum nocturnal SpO_2 (94.10 ± 3.31 vs. 96.15 ± 4.02, $P < 0.001$). In the group of patients with OHS, all had restrictive ventilatory defect with mean FEV_1/FVC of 79.57 ± 10.26. They had higher daytime sleepiness as assessed with ESS and higher scores with STOP-BANG questionnaire, though the difference was not statistically significant. Furthermore, there were no significant differences with regard to AHI.

Various previously known predictors of OHS such as BMI, AHI, daytime SpO_2, minimum nocturnal SpO_2, and spirometric parameters were analyzed for the prediction of OHS. Among them, univariate analysis between daytime $PaCO_2$ and other predictors showed that there was a significant correlation of $PaCO_2$ with BMI, FVC %predicted, FEV_1%predicted, minimum nocturnal SpO_2, and daytime SpO_2. Following stepwise multiple regression, minimum nocturnal SpO_2, FVC %predicted, and BMI were found to be independent predictors of OHS.

ROC curves were utilized to find out the threshold level of various predictors in predicting OHS. Table 3 demonstrates the various predictors of OHS including their threshold levels. Figure 2 illustrates the ROC curves for minimum nocturnal SpO_2, FVC %predicted, BMI, and daytime SpO_2 as predictors for the diagnosis of OHS. A minimum nocturnal SpO_2 threshold of 60% was most effective in detecting OHS with 90% sensitivity and 84.9% specificity. FVC %predicted threshold of 74.5% had 90% sensitivity and 52.8% specificity. With regard to the other predictors of OHS, BMI threshold of 30.9Kg/m^2 had a sensitivity of 90% and specificity of 43.4%. The daytime SpO_2 threshold of 95% had a sensitivity of 70% and specificity of 79.2% for detecting OHS.

For the gender differences in lung functions, ROC curves were separately analyzed for men and women to calculate

Table 3: Various predictors of obesity hypoventilation syndrome with their threshold levels

Predictor	Threshold level	Sensitivity (%)	Specificity (%)	AUC
Minimum nocturnal SpO_2 (%)	≤60	90	84.9	0.883
BMI (kg/m^2)	≥30.95	90	43.4	0.742
FVC% predicted	≤74.5	90	52.8	0.759
Daytime SpO_2	≤95.2	70	79.2	0.722
FVC absolute value (L)				
Male	≤2.33	50	81.6	0.548
Female	≤1.68	50	80	0.583

BMI: Body mass index, FVC: Forced vital capacity, SpO_2: Oxygen saturation by pulse oximetry, AUC: Area under curve

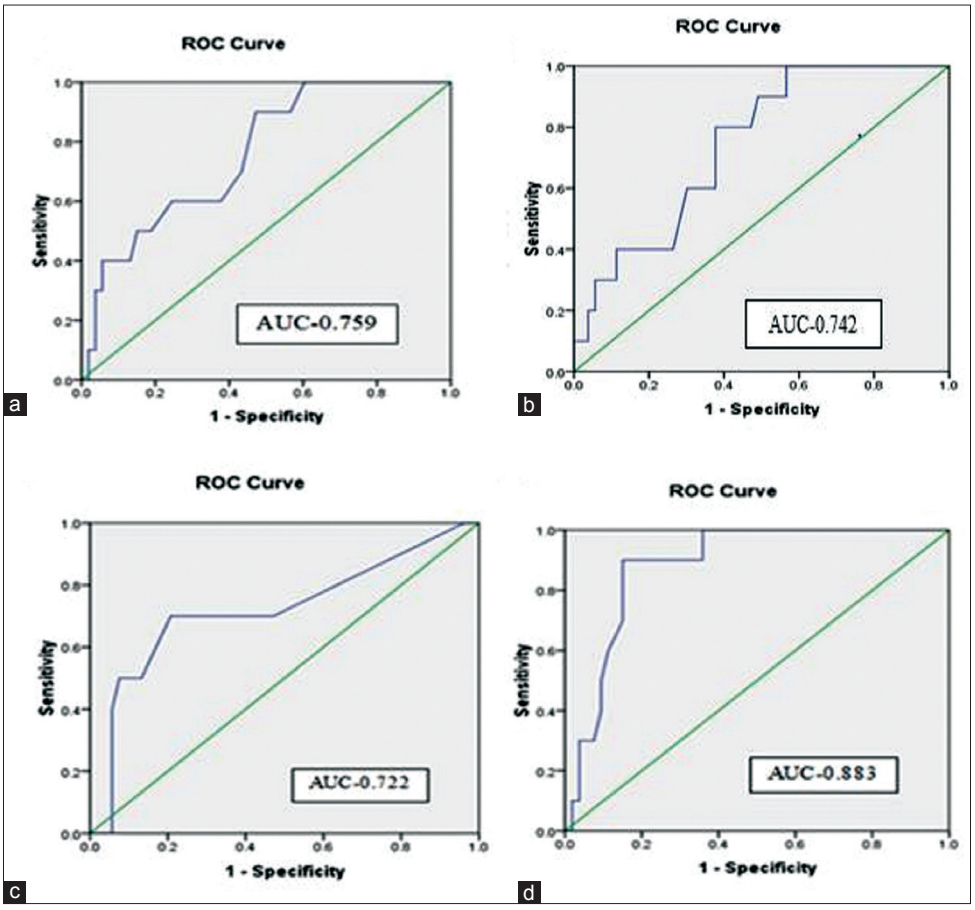

Figure 2: Receiver operating characteristic analysis for forced vital capacity %predicted (a), body mass index (b), daytime SpO_2 (c), and minimum nocturnal SpO_2 (d) as a predictors for the diagnosis of obesity hypoventilation syndrome

the gender-specific threshold levels of FVC absolute values [Figure 3]. We observed that the cutoff level of FVC was 2.33 L for men with specificity of 81.8% and sensitivity of 50% and 1.68 L for women with specificity of 80% and sensitivity of 50%.

DISCUSSION

The prevalence of OHS in India is not known. Our study is the first study in India to investigate OHS frequency and its predictors. OHS prevalence in our study was found to be 15.87% among SDB, which is similar to the Caucasian population.[7-9] There is variability regarding gender-specific prevalence in various studies, though most have reported a higher male prevalence. In our study, OHS was seen more frequently among women as compared to men. This was similar to the study by Nowbar *et al.*[11] and Mokhlesi *et al.*[18] The prevalence of OHS increased with increasing BMI. 100% of patients having BMI >50 kg/m^2 were detected to have OHS. Our results are consistent with previous studies.[5,7]

Ours is the first Indian study to find out the predictors of OHS. Our data showed a minimum nocturnal SpO_2 on polysomnography to be the most significant predictor. A threshold level of 60% had 90% sensitivity and 84.9% specificity in detecting OHS. Various other studies have also found minimum nocturnal SpO_2 as an independent predictor of OHS at various threshold levels. Bingol *et al.* showed a nadir SpO_2 cutoff of <80% to predict OHS with a sensitivity of 82.8% and a specificity of 54.5%.[19] Another study with a cutoff of 75.5% had higher specificity of 77.9%.[7] In our population, a lower cutoff of 60% had higher sensitivity and specificity for the detection of OHS.

We found a much lower cutoff of BMI, i.e., 30.95 kg/m^2, as a predictor of OHS. A study by Bülbül *et al.* in Caucasian population had shown that BMI >35 kg/m^2 was a predictor of OHS.[20] The variation may be due to the difference in morphology of different ethnic groups. The Japanese study by Akashiba *et al.*, involving 611 patients with OSA from 7 sleep centers, found that OHS may not be related to obesity alone as there was no significant correlation of BMI with daytime $PaCO_2$.[21] Although there is no direct comparison of Asian versus Caucasian patients having OHS, the craniofacial features have been studied regarding the development of OSA in both the populations. The Asian patients with OSA do have lower BMI and different cephalometric parameters compared to Caucasian.[21-24]

In patients with SDB, the presence of restricted lung volumes predisposes the patients to chronic respiratory failure and thus OHS. Hence, lung volumes, FVC in

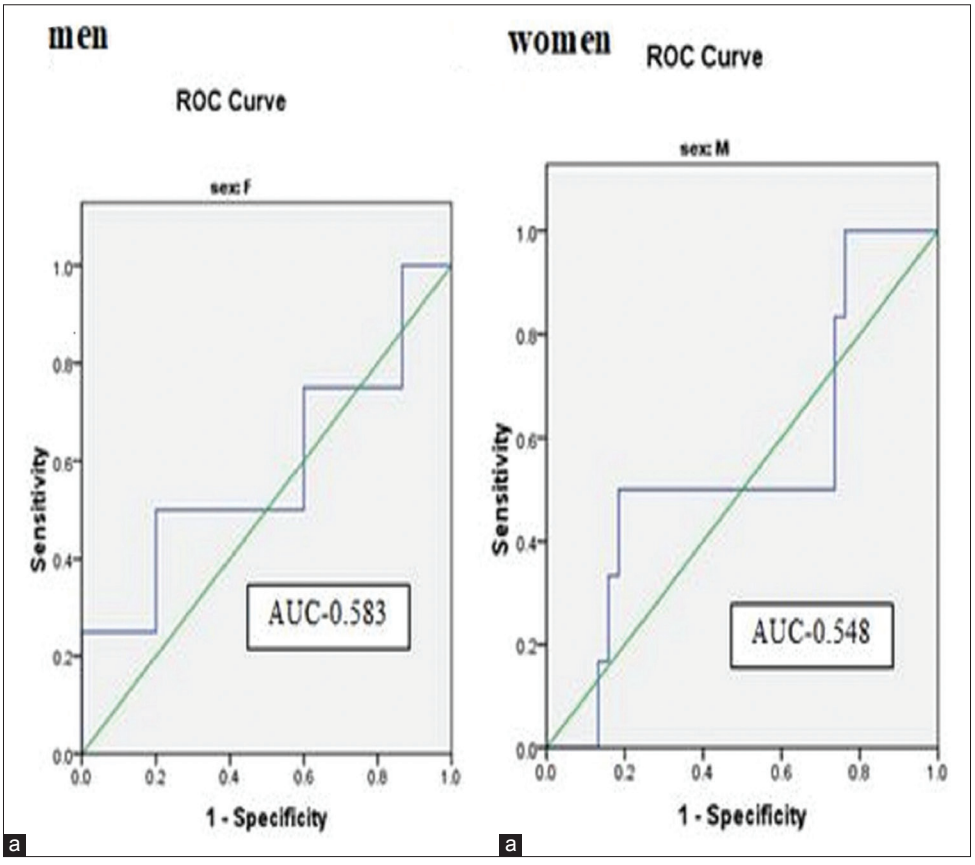

Figure 3: Receiver operating characteristic analysis for forced vital capacity (a), separated by gender, men (right) and women (left) as predictors for the diagnosis of obesity hypoventilation syndrome

particular, have been utilized in many studies as a predictor of OHS.[21,23] In our study also, the OHS group had restrictive ventilatory defect and significantly lower FVC %predicted compared to the non-OHS group as reported by previous studies.[3,7,21,25] However, none of the studies calculated any cutoff level to predict OHS. In our population, FVC %predicted of <74.5% was an important predictor of OHS with 90% sensitivity.

In order to have a maximal distribution and wider application of FVC, Mandal et al. have used absolute FVC in place of FVC% predicted values.[26] They have shown gender differences in FVC for the prediction of OHS. In their study, FVC <3.5 L for men and <2.3 L for women had high sensitivity to detect hypercapnia. Whereas, in our Indian patients, the cutoff for absolute FVC was lower at 2.33 L for men and 1.68 L for women. This can also be attributed to the racial and morphometric differences, with the Caucasian population having higher lung functions at baseline.[27-29]

In the present study, the daytime awake SpO_2 cutoff for detecting OHS was found at 95% which is in line with other studies.[7,30] Although the prevalence of OHS increased with increasing severity of OSA in our study, AHI was not found to be a predictor for OHS unlike other studies.[7,31] Furthermore, there was no significant difference in AHI between OHS group and non-OHS group. There are contradictory data on AHI as a determinant of OHS.[5,6,29]

The limitations of our study were its retrospective design and small sample size. Although the sample size was good enough for the statistical significance with a precision of 10%, inclusion of a larger sample would result in better precision of 5%.

CONCLUSION

The prevalence of OHS in Indian patients is similar to that of Caucasians. The predictors of OHS in Indian patients are minimum nocturnal SpO_2 <60%, FVC %predicted <74.5%, and BMI > 30.95 kg/m^2. The FVC cutoff of 2.33 L for men and 1.68 L for women is useful in predicting OHS. OSA patients with these parameters should be evaluated with ABG for the optimum management of SDB.

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Conflicts of interest
There are no conflicts of interest.

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