Background and Objectives: Chronic obstructive pulmonary disease (COPD) is a common airway disease that is frequently associated with comorbidities. In this study, we assessed the co-existence of obstructive sleep apnea (OSA) among patients with stable COPD. Methodology: This cross-sectional study included patients with stable COPD who were screened with Epworth’s Sleepiness Scale (ESS). Those with ESS score of >10 were subjected to in-lab polysomnography (PSG). PSG was manually analyzed and reported. Patients with apnea–hypopnea index of >5/h were diagnosed as OSA. Results: This study included 301 patients (78.1% male, 76.4% smokers, age 59.6 ± 10 years) with stable COPD. ESS score of >10 was observed in 47 (15.6%) patients. Among patients with ESS score of >10, OSA was observed in 34 (72.3%) patients. The overall prevalence of OSA among patients with COPD was 10.9%. Patients with co-existing OSA were older and had thicker neck and higher body mass index (BMI) as compared to COPD alone. In addition, patients with associated OSA had worse health-related quality of life (QOL) as shown by higher St. George’s Respiratory Questionnaire score (42.42 ± 7.22 vs. 25.22 ± 8.66; P < 0.001). Conclusions: Co-existing OSA is common among patients with COPD and has a significant adverse effect on the QOL. Among COPD patients, older age, thick neck, and high BMI may predict co-existing OSA and require PSG for the confirmation.

KEY WORDS: Chronic obstructive pulmonary disease, obstructive sleep apnea, overlap syndrome, quality of life, sleep apnea

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an important cause of impaired health-related quality of life (QOL) and poses an enormous burden in terms of morbidity and mortality, globally. COPD is the result of a slowly progressive and destructive process involving the lungs and airways that is poorly reversible with the currently available therapy. Hence, the disease is largely considered preventable, but remains only marginally treatable. COPD is frequently associated with comorbidities such as pulmonary hypertension (PH), malnutrition, anxiety, sleep-related disorders, osteoporosis, obesity, diabetes, metabolic syndrome, and others.

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These comorbidities are associated with increased risk of hospitalization and consumption of health resources. Frequently, these co-existing conditions can lead to mortality independent of respiratory failure. Hence, the management goals of COPD patients should also include active evaluation for the presence and appropriate treatment of comorbidities.

Obstructive sleep apnea (OSA) is another common disorder with reported prevalence of as high as 24% in some of the populations studied. OSA is associated with increased risk for cardiovascular diseases, poor health-related QOL, disability, and death. Interestingly, OSA and COPD share multiple risk factors such as obesity, smoking, increased airway resistance, and local and systemic inflammation. The coexistence of COPD and OSA is known as overlap syndrome. Both COPD and OSA are independently associated with increased risk of cardiovascular events; overlap syndrome may further increase this risk. Furthermore, patients with the overlap syndrome have higher incidence of COPD exacerbations and increased mortality compared with either COPD or OSA alone.

There are several possible mechanisms through which this increased risk may be explained. First, patients with overlap syndrome have more frequent hypoxemia and spend more time with hypercapnia during sleep. Second, apneic episodes are associated with more profound hypoxemia and increased frequency of cardiac arrhythmias. Finally, these patients are more likely to develop PH and heart failure. Use of continuous positive airway pressure (CPAP) therapy has been shown to break this vicious pathophysiological interaction.

Identification of overlap syndrome is the first step toward the management of this important health issue. There is limited data demonstrating the prevalence of COPD-OSA overlap syndrome. Hence, we planned this study to assess the prevalence, risk factors, and effects of OSA on health-related QOL among COPD patients.

**METHODOLOGY**

**Study design, settings, and patients**

Screening and recruitment of patients for this cross-sectional study was done at the outpatient department of a tertiary care teaching hospital between January and November 2014. The diagnosis of COPD was based on the Global Strategy for the Diagnosis, Management and Prevention of COPD (GOLD) guidelines. All adult patients (>45 years of age) who had stable symptoms and no change in COPD treatment for at least 4 weeks were eligible for participation in this study. Exclusion criteria for this study were use of medications known to interfere with the sleep (e.g., sedatives), CPAP or home oxygen; presence of psychiatric illness; previously diagnosed OSA; conditions expected to interfere with electroencephalogram (EEG), for example, brain tumor, epilepsy surgery; or refusal to participate in the study.

The study protocol was approved by the Institutional Ethics Committee of All India Institute of Medical Sciences, New Delhi (Ref no. IESC/T-88/28.02.2014). Written and informed consent was given by all the study participants.

**Evaluation of the patients**

Evaluation of the study participants included collection of data related to demography, clinical chemistry, clinical examination for features suggestive of PH (pedal edema, raised jugular venous pressure, loud second heart sound, hepatomegaly etc.), anthropometry, spirometry, screening for excessive daytime sleepiness, and polysomnography (PSG).

Anthropometric parameters recorded for this study included weight (in kg), height (in cm), body mass index (BMI), and neck circumference. Fasting blood glucose, cholesterol and thyroid-stimulating hormone (TSH), and clinical biochemistry including renal and liver function tests were obtained for all participants. Spirometry was performed using Medi-Soft Spiro air (S232) electronic spirometer (PK Morgan, UK) following previously published protocol by the American Thoracic Society on the standardization of pulmonary function testing.

**Screening with Epworth’s Sleepiness Scale**

All patients who fulfilled the inclusion criteria were screened for excessive daytime sleepiness using the Epworth’s Sleepiness Scale (ESS). Participants with an ESS score of >10 were classified as screening positive.

**Polysomnography**

Participants with ESS score of >10 underwent a standard sleep assessment using an attended, in-hospital, full-night PSG. Various parameters monitored during PSG included EEG; electro-oculogram; electro-cardiogram; chin and leg electromyogram; oral and nasal air flow; snoring, thoracic, and abdominal wall movements; body position; and transcutaneous oxygen saturation by finger pulse oximetry. One author (LN) manually scored the recordings using RemLogic or Somnologica software for sleep stages, apneas and hypopneas as per American Academy of Sleep Medicine recommendations. Patients with apnea–hypopnea index (AHI) of ≥5/h were diagnosed as having OSA.

**Health-related quality of life**

Health-related QOL assessment was done using St. George’s Respiratory Questionnaire’s (SGRQ) score in quiet and comfortable surroundings. All patients were instructed to answer all the questions completely and honestly. All three components of SGRQ (symptoms, activity, and impacts) were assessed, individually. Calculations were performed for scores of each component as well as total SGRQ score.

**Statistical analysis**

All continuous variables were expressed as mean ± standard deviation or median (interquartile
range). Frequency distribution and contingency tables were computed for categorical variables, as appropriate. To establish the association between each categorical factor, the comparisons between patients with and without OSA were done using Chi-square/Fisher’s exact test. The differences in means of SGRQ scores between participants with and without OSA were compared using the Student’s t-test.

For computation of OSA predictors, first, a series of univariate logistic regression were performed to identify factors that were associated with OSA. The association was quantified with unadjusted odds ratios and their 95% confidence intervals. A critical P value inferior to 0.15 and clinically important variables (demographic and laboratory) were chosen for further analysis. Step-wise multivariate logistic regression was performed using variables – gender, smoking status, presence of comorbidity, clinical evidence of PH, TSH, arterial pH, hypercapnia (PaCO$_2$ 45 mmHg), hypoxemia (PaO$_2$ <60 mmHg or SpO$_2$ <90%), and HCO$_3^-$, forced expiratory volume 1 (FEV$_1$) (% of predicted), neck circumference (>35.5 cm for male and >32.0 cm for female), age (>50 years), COPD GOLD stage-severe and very severe (III, IV), ESS Score (>10), BMI (>27.5 kg/m$^2$), and hypertension (systolic blood pressure >140 mmHg). Snoring and history of exacerbations were dropped from the multivariate analysis due to error in model convergence. A critical P value inferior to 5% was used for significance. All the data were analyzed using the STATA version 12.0 (StataCorp LP, College Station, TX 77845, USA) statistical software.

**RESULTS**

**Characteristics of the study cohort**

During the study period, a total of 301 patients with COPD were screened for the presence of OSA [Figure 1]. The study cohort consisted of predominantly smoker-men with normal BMI. Majority of the study patients had severe or very severe COPD and approximately quarter of them had one or more exacerbations treated with systemic corticosteroids during previous 1 year. Five (1.7%) patients had a history of road traffic accidents. At least one comorbidity was observed in 112 (37.2%) patients; systemic hypertension was the most common comorbidity. The demographic characteristics of the study population are summarized in Table 1.

**Prevalence of chronic obstructive pulmonary disease – Obstructive sleep apnea overlap**

Out of the 301 patients, 47 (15.6%) had excessive daytime sleepiness with ESS score of >10. Among these 47 patients, 34 were diagnosed with OSA following overnight PSG. Thus, the overall prevalence of OSA in our COPD study population was 10.9%. Among patients with excessive daytime sleepiness (ESS score of >10), OSA was observed in 70.2%. There were 10, 7, and 16 patients with mild (AHI 5–15/h), moderate (AHI 15–30/h), and severe (AHI >30/h) OSA, respectively.

**Predictors of obstructive sleep apnea**

We observed that patients with COPD-OSA overlap were older in age with BMI, neck circumference, and ESS significantly higher than patients without OSA. Comparison of other features is shown in Table 2.

**Table 1: Demographic profile of the study population**

| Characteristics | Observations |
|-----------------|-------------|
| Age (years), mean±SD | 59.6±10 |
| Male, n (%) | 235 (78.1) |
| BMI (kg/m$^2$), mean±SD | 23.7±6.1 |
| Neck circumference (cm), mean±SD | 35.9±6.4 |
| Smoking history, n (%) | 230 (76.4) |
| Smoking index, median (IQR) | 300 (200-600) |
| FEV$_1$ (percentage of predicted), mean±SD | 45.7±18.6 |
| GOLD stage, n (%) | 26 (8.6) |
| Stage 1 | 26 (8.6) |
| Stage 2 | 82 (27.2) |
| Stage 3 | 108 (35.9) |
| Stage 4 | 85 (28.2) |
| COPD duration (years), median (IQR) | 2.5 (1-5) |
| Number of exacerbations in last 1 year, median (IQR) | 1 (1-2) |
| Arterial blood gases (n=292), mean±SD | 7.38±0.07 |
| pH | 7.38±0.07 |
| PaCO$_2$ (mmHg) | 40.8 (17.75) |
| PaO$_2$ (mmHg) | 75.45 (27.33) |
| HCO$_3^-$ (mmol/L) | 25.8±6.8 |
| SPO$_2$ (%) | 93.8±7.1 |
| TSH (mIU/L), median (IQR) | 2.02 (1.2-3.1) |
| Snoring, n (%) | 22 (7.3) |
| ESS score, median (IQR) | 0 (0-4) |
| FBS, mg, mean±SD | 103.7±31.6 |
| Cholesterol (n=150), mg, mean±SD | 176.7±33.7 |
| SGRQ score (mean±SD) | 38.6±16 |
| Symptom component | 38.6±16 |
| Activity component | 33.4±11.3 |
| Impact component | 19.3±8.7 |
| Total score | 27.2±10.1 |

ESS: Epworth’s Sleepiness Scale, TSH: Thyroid-stimulating hormone, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, FEV$_1$: Forced expiratory volume in one second, SD: Standard deviation, FBS: Fasting blood sugar, SGRQ: St George’s Respiratory Questionnaire’s, IQR: Interquartile range

**Figure 1: Enrollment of the study participants**
Table 2: Comparison of the characteristics between patients with chronic obstructive pulmonary disease-obstructive sleep apnea and chronic obstructive pulmonary disease

| Parameters                        | With OSA (n=34) | Without OSA (n=267) | P     |
|-----------------------------------|-----------------|----------------------|-------|
| Age (years), mean±SD              | 60.15±9.84      | 55.5±10.44           | 0.01  |
| Gender, male (%)                  | 207 (77.53)     | 28 (82.35)           | 0.41  |
| BMI (kg/m²), mean±SD              | 33.4±5.41       | 22.47±5.02           | <0.001|
| Neck circumference (cm), mean±SD  | 39.4±2.07       | 33.52±1.05           | <0.001|
| Snoring, n (%)                    | 32 (94.12)      | 30 (11.24)           | <0.001|
| Smoking history, n (%)            | 24 (70.59)      | 206 (77.15)          | 0.72  |
| Smoking index, mean±SD            | 108.5±28.1      | 427.3±301.5          | 0.24  |
| GOLD stage, n (%)                 |                 |                      |       |
| Stage 1                           | 2 (6.1)         | 2 (14.3)             | 0.09  |
| Stage 2                           | 15 (45.5)       | 2 (14.3)             |       |
| Stage 3                           | 10 (30.3)       | 4 (28.6)             |       |
| Stage 4                           | 6 (18.2)        | 6 (42.9)             |       |
| COPD duration (years), mean±SD    | 4.17±4.50       | 2.84±2.63            | 0.16  |
| Systemic corticosteroid use, n (%)| 65 (24.34)      | 7 (20.59)            | 0.23  |
| Arterial blood gases (n=292), mean±SD |            |                      |       |
| pH                               | 7.32±0.07       | 7.38±0.07            | 0.16  |
| PaCO₂ (mmHg)                     | 49.02±23.89     | 44.41±16.76          | 0.15  |
| PaO₂ (mmHg)                      | 70.53±21.36     | 77.89±27.95          | 0.14  |
| HCO₃ (mEq/L)                     | 28.10±14.11     | 25.50±5.14           | 0.04  |
| SpO₂ (%)                         | 92.55±7.78      | 93.94±7.02           | 0.28  |
| TSH (muU/L), mean±SD             | 4.00±6.79       | 2.30±1.33            | 0.009 |
| FBS (mg), mean±SD                | 108.5±28.1      | 103.0±32.0           | 0.34  |
| Total cholesterol (mg), mean±SD   | 178.4±39.9      | 176.2±32.0           | 0.74  |
| ESS score, mean±SD               | 13.3±3.9        | 4.8±3.7              | <0.001|
| FEV₁/FVC, mean±SD                | 59.27±10.38     | 55.83±11.02          | 0.08  |
| FEV₁ (percentage of predicted), mean±SD | 49.86±18.48  | 45.21±18.56          | 0.17  |
| Actual FEV₁ (L), mean±SD         | 1.45±0.66       | 1.48±3.98            | 0.96  |
| Clinical evidence of pH, n (%)    | 29 (83.2)       | 63 (23.6)            | <0.001|
| PH on echocardiography, n (%)     | 5 (15.1)        | 1 (7.1)              | 0.50  |

PH: Pulmonary hypertension, ESS: Epworth’s Sleepiness Scale, TSH: Thyroid-stimulating hormone, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, FEV₁: Forced expiratory volume in one second, SD: Standard deviation, FVC: Forced vital capacity

Univariate analysis showed that age, FEV₁ (% predicted), BMI, neck circumference, evidence of PH, TSH, snoring, and ESS were associated with increased risk of OSA [Table 3]. However, multi-variable regression analysis revealed that only age, BMI, and neck circumference may predict OSA in the study participants [Table 3].

Impact of obstructive sleep apnea on chronic obstructive pulmonary disease

Individual components as well as total score assessed using SGRQ were significantly higher among the patients with COPD-OSA overlap. Patients with COPD-OSA overlap also had higher incidence of road traffic accidents and PH [Table 4].

**DISCUSSION**

In this single-center, cross-sectional study, we describe that OSA is common among patients with COPD. Older age, thick neck, and higher BMI may indicate the presence of associated OSA among patients with COPD. Co-existence of OSA and COPD both are highly prevalent disorders and hence just based on the chance association alone, the probability of co-existence in the general population would also be high. There have been previous attempts to describe the prevalence of OSA among COPD patients. Soler et al. reported prevalence of OSA of 62% among patients with moderate to severe COPD. Another large community-based study from Korea reported the prevalence of OSA in COPD as 45%. Overall, the reported prevalence of OSA in COPD is variable, ranging from 2.9% to 65.9%. Various factors associated with these variations in the prevalence of OSA in COPD may be attributed to the differences in populations studied, methods used for assessment of sleep (home or lab-based PSG, ESS, or Berlin’s questionnaire), and definitions (AHI >5/h and 10/h) used for the diagnosis of sleep apnea and sleep-disordered breathing (SDB). Recently, OSA is defined based on the AHI of >5/h. Hence, the description of prevalence of OSA diagnosis based on overnight PSG seems more relevant. However, considering the huge number, it is practically impossible to offer PSG to all patients with COPD. A protocolized approach involving an initial screening and ordering PSG only for patients identified as high-risk of sleep-related breathing disorders would be more practical and cost-effective way to diagnose OSA in the huge population of COPD. It is also well recognized that majority of the patients with sleep-related breathing disorders suffer with excessive daytime sleepiness. There are multiple questionnaire-based tools available for the detection of excessive daytime sleepiness in clinical settings. ESS is one such screening tool used for excessive daytime sleepiness. Our study has demonstrated that a significant number of patients with COPD had excessive daytime sleepiness. More importantly, OSA was present in three-fourths of patients with excessive daytime sleepiness (ESS >10). These results suggest that use of ESS can be used for the screening of excessive daytime sleepiness and OSA and may avoid the unnecessary use of PSG.

OSA, in general, is highly prevalent yet largely underdiagnosed condition. Co-existence of OSA may remain unnoticed as many of its symptoms indistinguishably overlap with COPD. Hence, the key to recognition is clinical suspicion based on some features or subjecting all these patients to PSG. Considering the humongous load of COPD, subjecting all these patients to PSG would neither be practical nor cost-effective. Therefore, risk stratification of patients with COPD for co-existing OSA may prove helpful. Older age, high BMI, and thick neck have been shown to be associated with OSA. Among patients with COPD, presence of systemic hypertension, hypercapnia, and PH has been described as indicators of associated OSA. Description of the cutoff values for clinical parameters that can be used for the risk stratification for the presence of OSA among
Table 3: Predictors of obstructive sleep apnea among chronic obstructive pulmonary disease

| Parameters                        | Unadjusted univariate | Multivariate |
|-----------------------------------|------------------------|--------------|
| Age                               | OR (95% CI)            | P            | OR (95% CI)  | P        |
| Age >50 years                     | 3.79 (1.79-8.01)       | 0.0007       | 8.18 (1.06-62.58) | <0.001 |
| Gender                            | 0.73 (0.29-1.96)       | 0.51         | -            | -        |
| GOLD class                        | 0.75 (0.52-1.10)       | 0.14         | -            | -        |
| FEV1 (percentage of predicted)    | 1.92 (1.01-3.64)       | 0.039        | -            | -        |
| COPD exacerbation                 | 2.09 (0.77-5.66)       | 0.14         | -            | -        |
| Smoking                           | 1.41 (0.63-3.10)       | 0.40         | -            | -        |
| Comorbidities                     | 1.00 (0.99-1.00)       | 0.59         | -            | -        |
| BMI                               | 1.36 (1.24-1.49)       | <0.001       | -            | -        |
| BMI >27.5 kg/m²                   | 75.88 (21.93-262.56)   | <0.001       | 1.21 (1.02-1.44) | <0.001 |
| Neck circumference                | 2.26 (1.60-3.19)       | <0.001       | 1.83 (1.24-2.69) | <0.001 |
| ECG cor pulmonale                 | 0.19 (0.06-0.61)       | <0.001       | -            | -        |
| PH on echocardiography            | 0.25 (0.15-0.42)       | <0.001       | -            | -        |
| Clinical evidence of PH           | 1.15 (0.25-5.21)       | 0.847        | -            | -        |
| TSH                               | 1.19 (0.96-1.48)       | 0.018        | -            | -        |
| ESS                               | 1.47 (1.33-1.62)       | <0.001       | -            | -        |
| ESS >10                           | 85.297 (29.29-248.33)  | <0.001       | -            | -        |
| Snoring                           | 126.4 (28.82-554.26)   | <0.001       | -            | -        |
| Hypertension                      | 1.70 (0.81-3.59)       | 0.16         | -            | -        |
| Hypoxemia                         | 1.08 (0.42-2.76)       | 0.87         | -            | -        |
| Hypocapnia                        | 0.75 (0.35-1.59)       | 0.46         | -            | -        |

PH: Pulmonary hypertension, OR: Odds ratio, CI: Confidence interval, ESS: Epworth’s Sleepiness Scale, TSH: Thyroid-stimulating hormone, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, FEV1: Forced expiratory volume in one second, ECG: Electrocardiographic

Table 4: Impact of obstructive sleep apnea on chronic obstructive pulmonary disease

| Parameters                        | With OSA (n=34) | Without OSA (n=267) | P  |
|-----------------------------------|-----------------|---------------------|----|
| SGRQ components, mean±SD          |                 |                     |    |
| Symptom component                 | 58.0±13.6       | 36.1±14.6           | <0.001 |
| Activity component                | 50.2±6.5        | 31.2±9.8            | <0.001 |
| Impact component                  | 32.3±7.3        | 17.6±7.3            | <0.001 |
| Total score                       | 42.42±7.22      | 25.22±8.66          | <0.001 |
| Number of patients required       | 8 (23.5)        | 61 (22.8)           | 0.94 |
| hospitalizations, n (%)           | 1.7±0.8         | 1.8±1.5             | 0.80 |
| Number of hospitalizations, mean±SD| 3 (8.8)        | 2 (0.75)            | 0.001 |
| Road traffic accident, n (%)      | 29 (83.2)       | 63 (23.6)           | <0.001 |
| Clinical evidence of PH, n (%)    | 5 (15.1)        | 1 (7.1)             | 0.50 |
| PH on echocardiography, n (%)     | 3.6 (11.5)      | 1.8 (6.1)           | <0.001 |

COPD patients is desired. Our study results suggest that OSA should be suspected among COPD patients who are older than >50 years of age with thick neck and high BMI.

In this study, we demonstrated that patients with COPD-OSA overlap have worse QOL as indicated by higher SGRQ score. In addition, more patients with COPD-OSA had road traffic accident and PH. Development of PH is associated with increased mortality among patients with COPD. Additional morbidity and increased risk of mortality among these patients. Hence, all COPD patients should be actively evaluated for the presence of OSA.

We recognize few limitations of this study. First, only patients with ESS of > 10 were subjected to PSG. Therefore, this study describes the prevalence of co-existing OSA among patients with COPD and excessive daytime sleepiness (sleepy OSA). Turceni et al. reported a significant correlation between AHI and ESS. The sensitivity of ESS to detect OSA has been shown to be as high as 79%. However, other studies have described that OSA can be seen in the absence of excessive daytime sleepiness. It is likely that we might have missed few patients of OSA either due to absence of the excessive daytime sleepiness or the limited sensitivity of ESS. Hence, subjecting all the study patients to PSG could have been the best approach to identify all patients of OSA, irrespective of excessive daytime sleepiness or ESS. Due to feasibility, we used PSG only among patients with excessive daytime sleepiness. Second, it should be noted that ESS has been used as a screening tool for excessive daytime sleepiness in the community and its utility among COPD is not known. In addition, this study made a diagnosis of OSA based on single-night PSG. Although considered as the “Gold Standard,” it is itself associated with few limitations: second-night PSG may detect additional 13% of patients with OSA. Few researchers have even proposed routine use of a second-night PSG in certain settings. Hence, whether repeating the PSG among the patients with COPD will also result in additional diagnosis of OSA among negative single-night study is still not known.

CONCLUSIONS

Co-existing OSA is common among patients with COPD and has significant adverse effects on the QOL. COPD patients who are older, have history of snoring, thick neck, and high BMI may be harboring co-existing OSA and require PSG for the confirmation.

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Conflicts of interest
There are no conflicts of interest.

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