European Review for Medical and Pharmacological Sciences 2018; 22: 4325-4331

Comorbidities in coexisting chronic obstructive pulmonary disease and obstructive sleep apnea – overlap syndrome

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Abstract. – OBJECTIVE: Chronic Obstructive Pulmonary Disease (COPD) and Obstructive Sleep Apnea (OSA) are separately associated with several comorbidities. The coexistence of the two diseases, referred to as overlap syndrome, may act as a predisposing factor for a higher prevalence of comorbidities compared to those associated with each disease separately. The objective of the study was to evaluate the relative prevalence of cardiovascular as well as other comorbidities, in patients with the overlap syndrome, as compared to patients that are diagnosed solely with OSA.

PATIENTS AND METHODS: We examined thirty-eight (38) patients (27 men, 11 women) with coexisting COPD and OSA – overlap syndrome (Group 1) *vs.* 38 patients with OSA-only (Group 2), matched for sex, age, and Body Mass Index (BMI). All patients underwent pulmonary function tests (PFTs), oximetry and overnight polysomnography and were asked about other coexisting chronic diseases and medications.

RESULTS: The two groups differed significantly, as expected, in PFTs (Forced Vital Capacity – FVC, p=0.005, Forced Expiratory Volume in 1 s – FEV_1, p<0.001) and in daytime oximetry (p=0.007). Three (3) overlap (7.89%) and 9 OSA patients (23.69%) had no other known diseases. All others suffered from 1 - ≥ 4 comorbidities. Overlap patients suffered more often from multiple (≥ 4) comorbidities than OSA-only patients (11, 28.95% *vs.* 4, 10.52%, respectively). The most common coexisting diseases were hypertension (50% *vs.* 42.1%), cardiovascular disease (CVD) (44.74% *vs.* 26.31%), diabetes mellitus (DM) (28.95% *vs.* 13.16%), dyslipidemia (21.05% *vs.* 26.31%) and depression (7.89% *vs.* 13.16%).

CONCLUSIONS: We conclude that comorbidities, especially cardiovascular, in patients with overlap syndrome are at least as prevalent as in sleep apneic only patients and may contribute to the overall severity and prognosis of the disease.

Key Words:
Chronic Obstructive Pulmonary Disease (COPD), Obstructive Sleep Apnea (OSA), Overlap syndrome, Comorbidities, Cardiometabolic risk.

Abbreviations
Chronic Obstructive Pulmonary Disease (COPD), Obstructive Sleep Apnea (OSA), Body Mass Index (BMI), Pulmonary Function Tests (PFTs), Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 s (FEV_1), Cardiovascular Disease (CVD), Diabetes Mellitus (DM), Venous Thromboembolism (VTE), C - Reactive Protein (CRP), Fast Fourier Transform Technique (FFT), Global Initiative For Obstructive Lung Disease (GOLD), Apnea-Hypopnea Index (AHI), American Academy Of Sleep Medicine (AASM), Positive Airways Pressure (PAP), Sleep Efficiency (SE), Total Sleep Time (TST), Non-Rapid Eye Movement (nREM), Rapid Eye Movement (REM), American Thoracic Society (ATS), European Respiratory Society (ERS).

Introduction

The 'overlap syndrome' was first described by Flenley[1] as the coexistence of COPD and OSA. COPD is defined as a preventable and treatable, systemic disease, characterized by air-flow limitation that is not fully reversible[2]. Spirometric criteria (FEV1 and ratio of FEV_1 to FVC, after bronchodilation < 0.70) are used to confirm the diagnosis and to assess the severity of the disease[2]. OSA is defined as multiple substantial decreases (hypopneas) or complete cessations (apneas) of airflow during sleep, despite increased effort to breathe, due to collapse of the upper airway, which lead to repetitive oxygen desaturations, brief arousals and sleep fragmentation[3]. Both diseases

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are characterized by severe clinical symptoms and are associated separately with significant comorbidities. The prevalence of overlap syndrome in adults aged 40 years and over is estimated about 0.5-1%[4].

Several researches[5,6] demonstrate that 86-98% of COPD patients have at least one comorbidity, with the average number per individual varying between 1-4. Comorbidities often contribute to dyspnea, limitation of exercise capacity, deterioration of quality of life, increased healthcare utilization and cost, and increased exacerbation and mortality risk[7,8]. Common comorbidities in patients with COPD include CVD (such as arterial hypertension, systemic venous thromboembolism (VTE), stroke, heart failure, coronary heart disease, arrhythmias and pulmonary hypertension), lung cancer and other cancers, psychiatric diseases (such as anxiety and depression disorders), metabolic conditions (such as malnutrition, obesity, diabetes mellitus, and dyslipidemia), anemia, osteoporosis, musculoskeletal dysfunction, sleep disorders and gastroesophageal reflux[7]. The enhanced chronic inflammatory response that starts in the airways and the lung at the beginning seems to affect peripheral organs as the disease progresses[7].

Various studies also indicate a causal relationship between OSA and hypertension, cardiovascular disease and diabetes mellitus[9-12], independently of concomitant risk factors such as obesity[13,14]. The chronic intermittent hypoxia and the sleep loss and fragmentation associated with OSA increase the levels of various markers of inflammation, like C-reactive protein (CRP), oxidative stress, and procoagulant and thrombotic activity[15,16]. These alterations may contribute to the development of endothelial and metabolic dysfunction, atherosclerosis and cardiovascular disorders associated with OSA[16]. Only pulmonary hypertension is a well-described comorbidity in the population, with a prevalence of 86% in overlap syndrome *vs.* 16% in OSA-only[17]. As published data are generally missing, our study aimed to further clarify the impact of comorbidities in overlap syndrome compared to OSA.

Patients and Methods

Patients

Thirty eight (38) patients (27 men, 11 women) with newly-diagnosed COPD and coexisting OSA – overlap syndrome – and 38 newly-diagnosed, OSA-only patients, matched for sex, age and BMI, were selected for the present study from our outpatient clinic in the Division of Pulmonology, Department of Clinical Therapeutics of the National and Kapodistrian University of Athens School of Medicine, at Alexandra Hospital of Athens, between 1st January 2014 to 30th June 2016. Our clinic is a general pulmonary division, of an internal medicine clinic that deals with all types of pulmonary diseases. The recruitment and the reassessment of the patients were done from one pulmonologist (Dr. G.T.). The research was performed according to the guidelines of the Declaration of Helsinki and informed consent was obtained from all individual participants included in the study. Ethical Committee approval was obtained by our hospital. COPD was diagnosed by history, physical examination, and standard pulmonary function tests according to the Global Initiative for Obstructive Lung Disease (GOLD) criteria[2]. Any patient who had dyspnea, chronic cough or sputum production, and/or history of exposure to risk factors for the disease underwent spirometry and static lung volumes measurement to confirm the presence of persistent airflow limitation. When COPD was stable, under optimal bronchodilation therapy according guidelines[2], patients were eligible to participate in the study. OSA was diagnosed as Apnea-Hypopnea Index (AHI) of ≥ 5 with associated symptoms or comorbidities or an AHI of ≥ 15, regardless of associated symptoms or comorbidities, according to American Academy of Sleep Medicine (AASM) diagnostic criteria[18]. Exclusion criteria were oxygen supplementation, other lung diseases, sleep disorders other than OSA, active or unstable cardiovascular diseases, non-controlled arterial hypertension, severe dementia, severe untreated psychiatric conditions and unwilling, undisciplined patient. BMI, neck, waist and hip circumferences were measured in the whole population. At baseline, each patient underwent detailed medical history – including the number, the type and the medications of other coexisting diseases -clinical examination, oximetry (model 8800, Nonin Medical, Inc., Plymouth, MN, USA), and PFTs (Master screen Diffusion, Jaeger, Germany): spirometry (pre/post bronchodilation). Whole-body plethysmography determination of static lung volumes was also performed only in COPD patients. A standard full-night polysomnography (PSG) was performed in each patient the same night of the initial evaluation (Alice, Respironics, Murrysville, PA, USA). Sleep records were manual-

ly scored, according to standardized criteria[19]. A second sleep study for manually Positive Airways Pressure (PAP) titration followed the next night. Appropriate PAP device and optimum pressure were defined as those that eliminated all respiratory events, arousals, and desaturation episodes and preserved $SaO_2 > 90\%$, according to standard titration rules[18].

Statistical Analysis

The values of all parameters were expressed by reporting the mean and standard deviation (M ± SD). A paired *t*-test and x^2-test of independence were conducted to compare parameters between the two groups. The post-hoc test used for validation was Tukey's honestly difference (HSD). A *p*-value less than 0.05 was considered as significant.

Results

We examined 38 newly diagnosed patients, 27 men and 11 women, with overlap syndrome and 38 patients with OSA-only. The two groups did not differ in terms of age, BMI, neck, waist and hip circumference (Table I). In overlap group, 12 patients (31.58%) were current smokers, 14 (36.84%) ex-smokers and 12 (31.58%) never smokers. In OSA group, 7 (18.42%) were current smokers, 12 (31.58%) ex-smokers and 19 (50%) never smokers. Also, none of the patients mentioned alcohol or other addictive substances abuse. As expected, overlap syndrome patients had significantly lower pulmonary function and daytime oxygen saturation due to COPD, when compared to OSA-only patients (Table I). The severity of airflow limitation was mild in 2 patients (5%), moderate in 28 patients (74%) and severe in 8 patients (21%). The two groups did not differ in terms of sleep efficiency (SE) and total sleep time (TST). Overlap patients slept more in Stage 2 sleep and had a longer REM sleep onset than sleep apneic (Table I). The total number of apneas and hypopneas, the AHI in non-rapid eye movement (nREM) and rapid eye movement (REM) sleep and the mean duration of respiratory events, did not differ significantly between the two groups, whereas the maximum duration of the events was longer in OSA compared to overlap syndrome (Table I). Finally, between the two groups, mean oxygen saturation was lower in overlap patients, and minimum oxygen saturation was lower in OSA patients (91.15 ± 2.76 *vs.* 92.4 ± 2.8, $p = 0.004$ and 80.08 ± 6.87 *vs.* 79.11 ± 8.58, $p = 0.004$, respectively, Figure 1).

Table I. Baseline characteristics, respiratory function and sleep data of the two populations.

	Overlap Syndrome (COPD + OSA)	OSA	*p*-value
Age (years)	67±8.75	67±9.22	0.666
BMI (kg/m^2)	35.45±8.52	34.73±7.93	0.708
FVC (%)	70.87±14.22	87.05±14.3	**0.001**
FEV_1 (%)	62.31±14.4	91.96±14.11	**0.001**
FEV_1/FVC	70.80±8.67	83.15±5.15	**0.001**
PEF (%)	64.43±20.35	83.57±22.57	**0.001**
SaO^2 (%)	94.75±2.37	96.13±1.56	**0.007**
TST (min)	241.68±92.37	229.73±104.73	0.6
SE (%)	77.17±17.95	76.55±18.86	0.885
N1 (min)	33.28±37.8	29.23±35.55	0.41
N2 (min)	145.42±78.09	126.17±80.41	**0.045**
N3 (min)	34.14±37.94	46.44±56.24	0.096
REM (min)	20.05±21.02	27.43±31.76	0.098
Apneas + Hypopneas (n)	184.29±125.18	159.95±89.06	0.332
AHI nREM	54.96±32.74	48.56±28.49	0.39
AHI REM	47.1±30.71	43.43±20.22	0.26
AI	19.02±18.46	21.87±18.52	0.575
Mean duration of events (s)	21.4±5.62	21.97±5.98	0.08
Max duration of events (s)	53.35±18.01	57.26±23.13	**0.021**

Abbreviations: AHI: Apnea-Hypopnea Index, AI: Arousal Index, BMI: Body Mass Index, FVC: Forced Vital Capacity, FEV_1: Forced Expiratory Volume in 1sec, PEF: Peak Expiratory Flow Rate, SaO_2: Oxyhemoglobin Saturation, TST: Total Sleep Time, SE: Sleep Efficiency, N1: Stage 1, N2: Stage 2, N3: Stage 3-4, REM: Rapid Eye Movement.

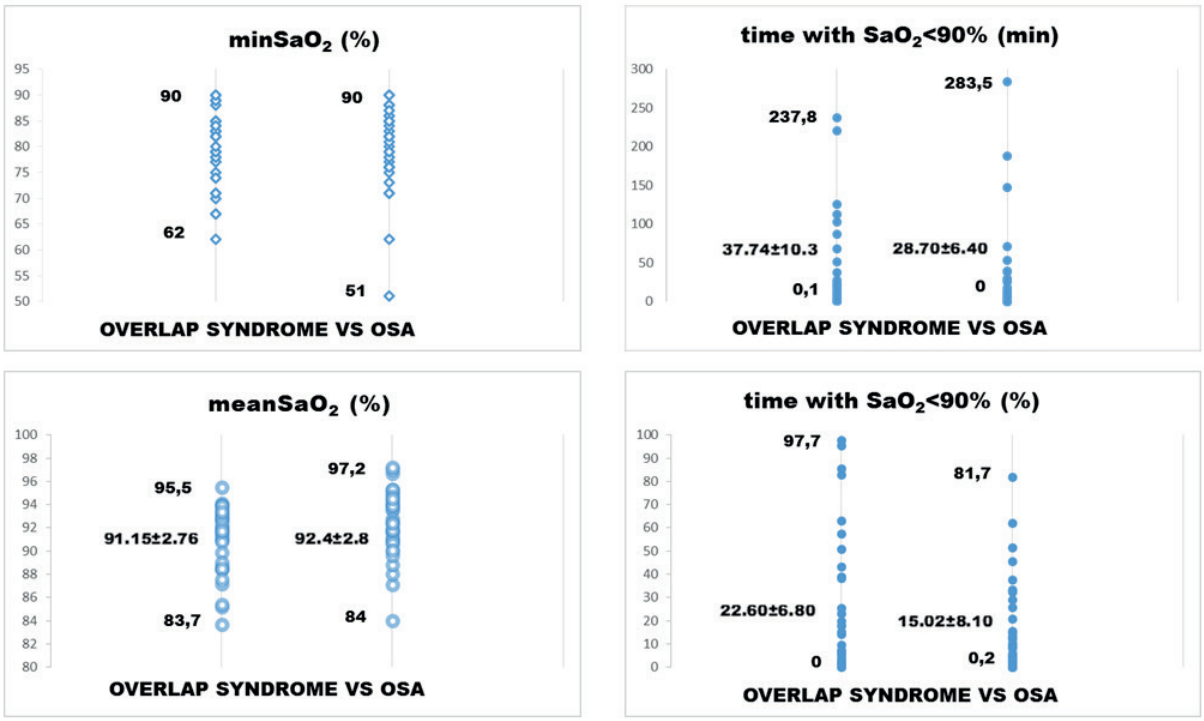

Figure 1. Oxygenation during sleep (mnimum and Mean SaO_2, Time spen in SaO_2<90%), in each group.

Time spent in SaO_2 < 90% and arousal index did not differ significantly between the two groups. Overlap patients often needed supplementary oxygen to the PAP device in order to achieve an adequate SaO_2 > 90% during sleep. Several comorbidities (≥ 4) were more often observed in overlap patients than in sleep apneic patients (92.11% *vs.* 76.31%, respectively). Furthermore, overlap patients suffered more often from multiple comorbidities (≥ 4) than sleep apneic patients (28.95% *vs.* 10.52%, respectively). The most prevalent comorbidities were hypertension, cardiovascular disease (CVD), DM, dyslipidemia and depression (Figure 2). Hypertension, CVD and DM were more common in overlap than in sleep apneic patients, whereas dyslipidemia and depression were more common in OSA-only when compared to overlap syndrome. All other comorbidities are presented in Table II. Even though results indicated a slight trend towards a higher likelihood of multiple comorbidities being present in the overlap group, the difference that was observed, compared to the OSA-only, did not manage to reach statistical significance. Also, no prevalent association was elucidated between the number and/or the type of comorbidities and AHI and nocturnal oxygenation indices of the study population.

Discussion

To our knowledge this is the first study evaluating the impact of comorbidities in overlap syndrome. Although, both COPD and OSA are associated independently with several coexisting diseases, data about the number and/or the type of comorbidities in overlap population are missing. Our work demonstrated that overlap patients suffered more often from multiple comorbidities compared to sleep apneic patients, matched for sex, age and BMI. Cardiometabolic diseases, like hypertension, CVD, DM and dyslipidemia were more frequent, though other diseases, such as depression, gastroesophageal reflux, hyperuricemia, cancer, Parkinson disease, dementia, osteoporosis etc. were also present. However, the difference between the number and/or the type of comorbidities did not reach a statistically significant level.

Flenley[1] first described the overlap syndrome in 1985 as the coexistence of COPD and OSA in an individual and suggested polysomnography for COPD patients with nocturnal oxygen desaturation who developed morning headaches when treated with nocturnal supplemental oxygen. Later, the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines suggested that mild COPD patients with daytime hypoventilation

Table II. Type of comorbidities in the two groups.

Type of Comorbidity	Overlap syndrome (n, %)	OSA-only (n, %)
Gastroesophageal reflux	5 (13.16)	1 (2.63)
Hyperuricaemia	4 (10.53)	1 (2.63)
Diseases of thyroid gland	2 (5.26)	8 (21.05)
Parkinson disease	2 (5.26)	1 (2.63)
Benign hypertrophy of prostate gland	2 (5.26)	3 (7.89)
Dementia	1 (2.63)	2 (5.26)
Cancer	2 (5.26)	-
Epilepsy	1 (2.63)	-
Osteoporosis	1 (2.63)	-
Glaucoma	-	1 (2.63)
Adenoma of parathyroid glands	1 (2.63)	1 (2.63)
Myasthenia	1 (2.63)	-
Chronic renal insufficiency	1 (2.63)	-
Adamantiadi – Bechet syndrome	-	1 (2.63)
Retroperitoneal fibrosis	1 (2.63)	-

or evidence of pulmonary hypertension should be referred for polysomnography[20]. Pulmonary hypertension is still the best described comorbidity in this population[17], whereas little published evidence exists about other comorbidities. COPD is a systemic disease that often coexists with other diseases such as CVD, hypertension, DM, depression, osteoporosis, cancer, and gastroesophageal reflux[2,21]. According to recent studies[21], while hypertension is the most frequently occurring comorbidity, CVD is not only pervasive (≈ 30%) but also the most important coexisting disease in COPD as it affects mortality[2]. Furthermore, metabolic dysfunction and diabetes type 2 are also associated with reduced lung function[21]. These data from the literature are in accordance with ours – previous unpublished data - in 32 COPD patients; 87.5% of patients suffered from ≥ 1 comorbidities, with CVD and metabolic disease most frequently observed in this population (68.8% and 53.1%, respectively)[22]. Some of these comorbidities (pulmonary artery disease and malnutrition) are directly caused by COPD (secondary to COPD), whereas others share common risk factors, like smoking

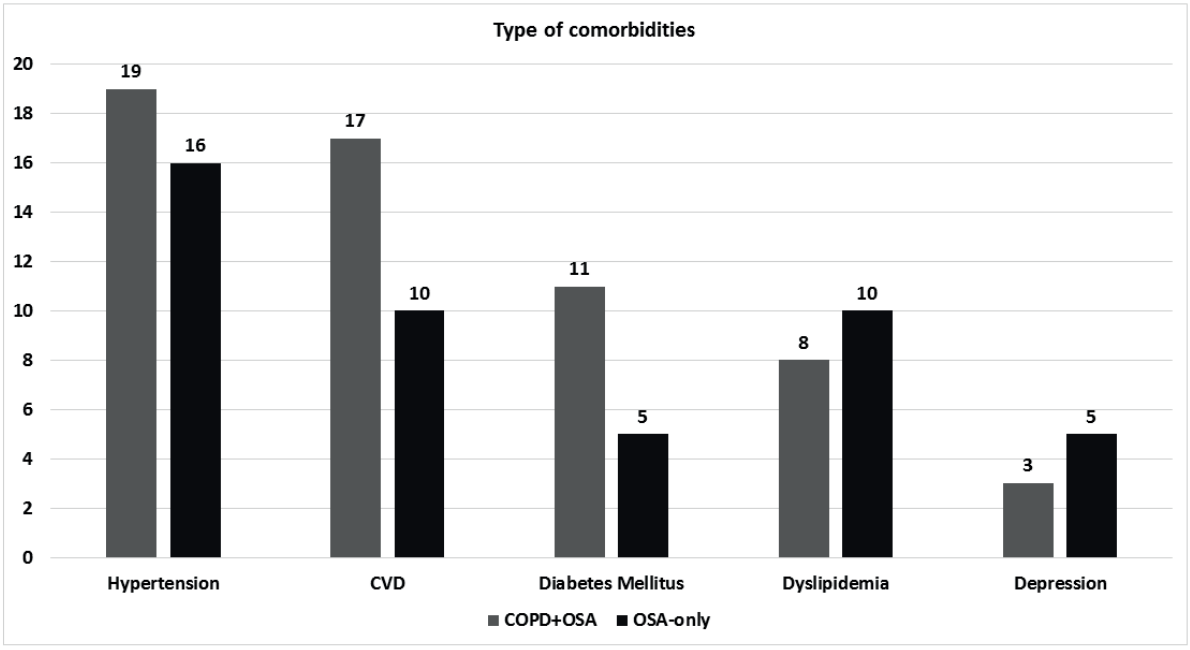

Figure 2. Most prevalent comorbidities in the two groups.

and other lifestyle factors (place of work, air pollution etc.) and genetic susceptibility, are associated with similar pathophysiological mechanisms, like airway, systemic inflammation, lung hyperinflation, endothelial dysfunction and oxidative stress[7]. OSA is also considered a systemic disease that often coexists with other diseases such as CVD, hypertension, DM, depression, and cognitive impairment[3]. More specifically, an apnea-hypopnea index > 20.6 events per hour of sleep is associated independently with the presence of hypertension, diabetes, metabolic syndrome, and depression[14]. About 50% of OSA patients are hypertensive and one third suffers from CVD[23]. Also, the prevalence of DM is approximately 30% in OSA patients[24]. Breathing cessation, nocturnal hypoxia, continuous brief arousals and sleep fragmentation could activate the sympathetic system and the HPA axis, trigger low-grade inflammation, oxidative stress and endothelial dysfunction, and promote insulin resistance[25]. When both COPD and OSA coexist in overlap syndrome it is possible to hypothesize that the consequences may be multiplied due to additive, underlying pathophysiological mechanisms – mainly hypoxia and sleep fragmentation during sleep. Indeed our overlap patients suffered from multiple comorbidities. Also, the type of comorbidities had similar distribution in both overlap and OSA population: the 1st most common disease was hypertension[26], followed by CVD (2nd) and DM (3rd). Probably, the two diseases share common mechanisms. However, the number and/or the type of comorbidities did not differ to the level of statistical significance. Moreover, AHI and indices of hypoxia were not associated with coexisting diseases. Consequently, underlying pathophysiological mechanisms in patients with either OSA or COPD may not be further enhanced when COPD and OSA occur together. According to a recent study, neural respiratory drive from wakefulness to stage 2 sleep increased in patients with OSA, but decreased in those with COPD, suggesting that OSA can partially compensate for reduction of neural respiratory drive inherent to COPD and certainly does not seem to worsen hypoventilation associated with COPD[27]. Those data agree with our findings, in the present study, in which the two groups did not differ significantly in terms of time spent in SaO_2 < 90% and arousal index. He et al[26] suggested that the COPD-associated decrease in drive is cancelled out by the OSA-associated increase in it and consequently OSA is protective against sleep-related hypoventilation in COPD. Possibly, two bad things like COPD and OSA can be good for the patient, as reported by Laghi et al[28]. Our study had several limitations. The sample of the two populations was small. Furthermore, we evaluated the coexistence of two heterogeneous disorders, COPD and OSA. Both diseases are characterized by different clinical outcomes and prognosis, despite similar airway obstruction or apnea – hypopnea index. Moreover, some of our COPD patients had spirometric values affected by obesity, which were not in total accordance with the GOLD criteria. However, this could also be attributed to increased BMI, as a recent study indicated that the ratio of FEV1/FVC increased by 0.04 in men and 0.03 in women, when BMI increased by 10 units (kg/m^2)[29]. The authors suggested that the accurate diagnosis of airway obstruction is significantly less likely in subjects with BMI $\geq$ 25 kg/m^2, and COPD can go underdiagnosed and undertreated among overweight and obese individuals[29]. We did not estimate the exact impact of BMI in FeV1/FVC ratio of our COPD patients. Finally, we did not measure markers of inflammation, like CRP.

Conclusions

We showed that the greater proportion of overlap patients suffer from several comorbidities. The most common comorbidity is hypertension, followed by CVD and DM. However, overlap when compared to sleep apneic patients - matched for sex, age, and BMI – did not differ significantly in number and/or type of comorbidities. Further larger studies are required to evaluate the impact of comorbidities in overlap syndrome, as well as possible underlying - synergic or protective - mechanisms between COPD and OSA.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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