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Letter to the Editor

Prevalence and determinants of co-morbidities in patients with obstructive apnea and chronic obstructive pulmonary disease

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The coexistence of obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) has been described as the "overlap syndrome" (OS) [1]. Compared to patients with simple OSA, patients with OS exhibit a lower nocturnal oxygen saturation (SaO_2), more profound desaturations during the apneic events and often severe hypoventilation particularly during rapid-eye-movements sleep [2].

It is now clear that some physiological pathways, strictly associated with cellular hypoxia, are shared by OSA and COPD [1]. Systemic inflammation and altered autonomic balance are present in both diseases and may increase the cardiovascular risk [1,3]. Although it is hypothesized that the presence of cardiovascular complications may be one of the factors determining poor outcomes, few data are so far available on the burden of morbidities in the overlap syndrome. The aim of this study was to evaluate the prevalence of chronic diseases in patients with OSA or overlap syndrome and to assess factors affecting the risk of single or multi-morbidity.

We conducted a retrospective observational study in a group of 295 consecutive patients with OSA, and 219 with OS referred to our Sleep Laboratory. Standard polygraphy was performed as previously described [4] and automatic/manual analysis performed according to standard criteria [5]. Obstructive apneas were defined as a drop in peak signal excursion > 90% of pre-event baseline with a duration > 10 s in the presence of abdominal and thoracic movements. Hypopneas were defined as a reduction in flow ≥30% with > 3% oxygen desaturation or arousal, in the presence of abdominal and thoracic movements [5]. We made diagnosis of OSA when the apnea-hypopnea index (AHI), which is the number or respiratory events per hour, was > 10. T90 SaO_2 was the time of the night spent with SaO_2 below 90%. In all patients we performed standard spirometry. The diagnosis of COPD was obtained by the clinical history and confirmed by spirometry. The severity of airflow limitation was classified according to the GOLD guidelines [6]. Patients with OSA and confirmed diagnosis of COPD were included in the OS group. Reviewing clinical records, we collected demographic data and the presence of co-morbidities focusing on hypertension, cardiovascular diseases (ischemic disease, heart failure, arrhythmias, etc), cerebrovascular diseases, metabolic disorders (diabetes mellitus, thyroid disorders) and gastro-esophageal reflux (GER). We also included scores obtained by the Epworth Sleepiness Scale (in order to measure sleepiness) and the Mallampati score (which relates tongue size to pharyngeal size). The protocol was approved by the local ethical committee.

Descriptive statistic was used for demographic data, which are presented as mean ± standard deviation (SD). To compare two categorical variables, we used the chi-square test (χ^2). We performed multivariate logistic regression analysis in order to establish risk factors for each co-morbidity and to calculate the Odd Ratio value.

Demographic and clinical data of the groups are shown in Table 1. Significant differences in polygraphic data were observed between patients with OSA and OS during sleep. Although the AHI values were similar in the two groups (45 OSA and 44.8 OS), patients with OS exhibited a more pronounced nocturnal hypoxemia in terms of both mean SaO_2 (90% OSA *vs* 88% OS) and T90 SaO_2 (22.8 OSA *vs* 45.0 OS) (Table 1).

Hypertension, diabetes mellitus, cardiovascular diseases and GER were common in both OSA and OS patients. Conversely, we found a prevalence < 10% (2% OSA and 6% OS) for cerebrovascular diseases. Hypertension was the most common disease in all groups with a significantly higher prevalence in OS (54.3%) compared to OSA (45%), $P < .05$, followed by cardiovascular diseases documented in 35.6% of patients with OS and 17.5% with OSA, $P < .001$. Diabetes was also more prevalent in OS (20%) than in OSA (12.5%), $P < .05$. No significant difference was found in the prevalence of GER (OSA 18%, OS 13%, P= NS). In the group of patients with OS we found that hypertension and cardiovascular diseases were more common among patients with severe COPD (GOLD III/IV) compared with mild to moderate COPD (GOLD I/II).

In order to understand whether the presence of COPD or other factors could increase the risk of a single morbidity or multi-morbidity (concomitant hypertension, cardiovascular disease and diabetes) we performed a multivariate logistic regression analysis. In the model we included age, sex, BMI, smoking status and the presence of COPD as independent variables. Age and COPD predicted the presence of hypertension and cardiovascular diseases, but not diabetes (Table 2). Age and COPD were particularly relevant in predicting the risk of cardiovascular diseases (Odd Ratio 4.03 for age and 2.34 for COPD). In addition, both age and COPD strongly predicted the occurrence of multimorbidity (Odd Ratio 7.6 for age and 6.72 CI COPD) (Table 2).

Taken together these results indicate that in patients with the overlap syndrome the burden of chronic conditions is greater than in those with simple OSA. This is due in part to the older age of these

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Table 1
Demographic, clinical and polygrahic data of the study groups.

	OSA (295)	Overlap (219)	*P* value
Males, %	77	77	ns
Age, yrs	57 ± 12	66 ± 10	< 0.001
Body Mass Index, Kg/m2	35.5 ± 11.3	33.4 ± 7.3	< 0.05
Current smoker, %	34	46	< 0.05
FEV_1,% predicted	83	56	< 0.001
Awake SaO_2, %	93.6 ± 6.0	91.7 ± 7.9	< 0.001
Airflow limitation			
GOLD 1, % of patients		15.9	
GOLD 2, % of patients		40.0	
GOLD 3, % of patients		27.8	
GOLD 4, % of patients		15.5	
AHI	45.0 ± 21.3	44.8 ± 21.0	ns
Mean nocturnal SaO_2, %	90.7 ± 7.0	88.5 ± 7.1	< 0.001
SaO_2 T90,	22.8 ± 10.0	45.0 ± 26.8	< 0.001
ESS	9.4 ± 4.9	9.6 ± 4.7	< 0.05
Mallampati score	3.2 ± 0.7	3.09 ± 0.9	ns

FEV_1: forced expiratory volume in 1 s. AHI: apnea/hipopnea index. ESS: Epworth Sleepiness Scale. GOLD: Global Initiative for Chronic Obstructive Lung Disease.

Table 2
Adjusted odd ratios obtained by multivariate logistic regression analysis for different co-morbidities and multi-morbidity.

	ODD ratio	95% CI	P value
Hypertension			
Age	3.84	2.31–6.40	< 0.0001
Sex	1.00	0.61–1.64	ns
BMI	1.03	0.40–2.66	ns
COPD	1.43	0.93–2.13	< 0.05
Smoking	0.82	0.54–1.23	ns
CV diseases			
Age	4.15	1.91–9.03	< 0.0001
Sex	1.39	0.82–2.35	ns
BMI	0.55	0.21–1.45	ns
COPD	2.27	1.45–3.55	< 0.0001
Smoking	1.61	1.03–2.52	< 0.05
Diabetes			
Age	1.03	0.55–1.93	ns
Sex	0.98	0.53–1.82	ns
BMI	1.23	0.35–4.38	ns
COPD	1.22	0.73–2.02	ns
Smoking	2.27	1.38–3.73	< 0.05
Three co-morbidities			
Age	7.8	4.86–11.29	< 0.001
Sex	1.77	1.08–4.05	ns
BMI	0.54	0.31–0.89	ns
COPD	6.17	4.09–10.81	< 0.05
Smoking	2.21	1.12–3.70	ns

CV = cardiovascular diseases, BMI = Body Mass Index, COPD = chronic obstructive pulmonary disease, CI = confidence interval.

patients, but also to the fact that COPD *per se* increases the risk of morbidity. In particular, the concomitant presence of COPD in patients with OSA significantly doubles up the risk of cardiovascular diseases and produces a 6-fold increase in the risk of multi-morbidity.

In agreement with previous reports, we found that patients with OS experienced a more profound nocturnal hypoxemia, compared to simple OSA, although the AHI was similar in the two groups [1,]. Severe nocturnal hypoxemia, associated with COPD, determines chronic pulmonary hypertension and the simultaneous presence of OSA has a synergistic/additive negative effect on pulmonary hemodynamics [7,8]. A higher cardiovascular mortality rate in OS compared to OSA has also been shown [7]. Lacedonia and co-workers recently reported a greater prevalence of multi-morbidity in OS than in OSA [9], however it was unclear whether confounding factors (age or BMI) affected the risk of morbidity. In our study we found that the older age and the presence of COPD were independent factors predicting the risk of co-morbidities. Interestingly, in a population of patients with OSA > 50 years old Marrone and co-workers found that the presence of co-morbidities predicted all causes mortality, independently from the severity of OSA [10]. Our findings suggest that the co-existence of COPD, determining a 6-fold increase in the risk of multi-morbidity, may further increase the risk of mortality in patients with OSA. However, this is only a speculation, as we do not have a follow up of the patients. In conclusion, we found that the burden of morbidities is higher in the overlap syndrome compared to simple OSA due to the older age of the patients and to the effect of COPD *per se.* This morbidity burden is likely to produce adverse outcomes, such as increased mortality, poor quality of life and increased health care utilization.

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References

[1] McNicholas WT. COPD-OSA overlap syndrome: evolving evidence regarding epidemiology, clinical consequences, and management. Chest 2017 Dec;152(6):1318–26.
[2] Chaouat A, Weitzenblum E, Krieger J, Ifoundza T, Oswald M, Kessler R. Association of chronic obstructive pulmonary disease and sleep apnea syndrome. Am J Respir Crit Care Med 1995 Jan;151(1):82–6.
[3] Ryan S, Taylor CT, McNicholas WT. Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. Circulation. 2005;112(17):2660–5.
[4] Spicuzza L, Bernardi L, Balsamo R, Ciancio N, Polosa R, Di Maria G. Effect of treatment with nasal continuous positive airway pressure on ventilatory response to hypoxia and hypercapnia in patients with sleep apnea syndrome. Chest 2006;130(3):774–9.
[5] American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed Darien, IL: American Academy of Sleep Medicine; 2014.
[6] Global initiative for chronic obstructive lung disease: The global strategy for the diagnosis, management and prevention of COPD. http://www.goldcopd.org/; 2017.
[7] McNicholas WT. Comorbid obstructive sleep apnoea and chronic obstructive pulmonary disease and the risk of cardiovascular disease. J Thorac Dis 2018;10:S4253–61.
[8] Sharma Bhavneesh, Neilan Tomas G, Kwong Raymond Y, Mandry Damien, Owens Robert L, McSharry David, et al. Evaluation of right ventricular remodeling using cardiacmagnetic resonance imaging in co-existent chronic obstructive pulmonary disease and obstructive sleep apnea. COPD 2013;10(1):4–10.
[9] Lacedonia D, Carpagnano GE, Patricelli G, et al. Prevalence of comorbidities in patients with obstructive sleep apnea syndrome, overlap syndrome and obesity hypoventilation syndrome. Clin Respir J 2018 May;12(5):1905–11.
[10] Marrone O, Lo Bue A, Salvaggio A, Dardanoni G, Insalaco G. Comorbidities and survival in obstructive sleep apnoea beyond the age of 50. Eur J Clin Invest 2013;43(1):27–33.

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