Is sleep disordered breathing a risk factor for COVID-19 or *vice versa*?

Received: 18 Jan 2022
Accepted: 8 Feb 2022

To the Editor:

Sleep is a physiologically invigorating, mostly nocturnal state, that plays an important role in the empowerment of the immune system [1]. Obstructive sleep apnoea (OSA) is the most frequent form of sleep disordered breathing (SDB) [2], which may represent a relevant risk factor for the clinical course and prognosis of coronavirus disease 2019 (COVID-19) [3, 4]. Common characteristics and comorbidities of OSA and COVID-19 (male gender, age >60 years, metabolic syndrome, cardiovascular and chronic pulmonary disease) were recently described as prognostic factors in COVID-19 [5]. However, the prevalence of SDB after COVID-19 remains insufficiently explored.

This study included 58 patients who fulfilled the following criteria: age >18 years, a positive PCR test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), pulmonary infiltrates on chest computed tomography (CT) scan and a need for hospitalisation due to COVID-19 during the period from 8 March to 1 May 2020 [6]. The absence of written informed consent and/or the presence of a positive airway pressure (PAP) therapy were exclusion criteria. At the time of hospitalisation, all patients received treatment according to the local guidelines and were classified according to the World Health Organization (WHO) Ordinal Scale for Clinical Improvement. For the analysis, we classified the patients into a mild/moderate (n=27) and a severe COVID-19 group (n=31) (table 1). Severe COVID-19 was defined by oxygen saturation <93%, respiratory rate >30 breaths per min, C-reactive protein levels (CRP) >75 mg·L^{-1}, extensive area of ground-glass opacities or progression on CT during hospitalisation [6].

Demographic, clinical and outcome data were collected prospectively. Pulmonary function testing, including whole-body plethysmography and carbon monoxide diffusion capacity (Vyntus BODY; Vyaire Medical, Höchberg, Germany), as well as home sleep apnoea testing (HSAT) with the WatchPAT200 (Itamar Medical Ltd., Caesarea, Israel) were conducted 3–12 months (mean±SD 5.26±3.08 months) after discharge. WatchPAT200 measurements and analyses are standardised, validated and recommended as a diagnostic tool for OSA according to the American Academy of Sleep Medicine (AASM) clinical practice guidelines [7]. Sleep apnoea severity was graded: mild (apnoea–hypopnoea index (AHI) 5–14 events·h^{-1}), moderate (AHI 15–30 events·h^{-1}) and severe (AHI >30 events·h^{-1}). Daytime sleepiness was evaluated with the Epworth Sleepiness Scale (ESS).

The patient cohort, consisting mainly of males (74%) of Caucasian ethnicity (90%), presented at admission with a mean±SD age of 59.84±13.79 years and mean±SD CRP level of 72.80±65.87 mg·L^{-1}. The initial quantification of radiological lung involvement with pulmonary infiltrates at admission was 15.47±11.06% of total lung volume. Next to the WHO scale, the following parameters were significantly different between the mild/moderate and severe COVID-19 groups: CRP levels (p=0.005), lymphocyte count (p=0.043), the percentage of radiological lung involvement (p=0.034) as well as the length of hospital stay (p<0.0001).

At follow-up, six patients (10.3%) presented with obstruction (forced expiratory volume in 1 s (FEV_1)/forced vital capacity <70%), three patients (5.2%) with restriction (total lung capacity (TLC) <80% of predicted), and 20 patients (34.5%) with diffusion impairment (diffusing capacity of the lung for carbon monoxide (D_{LCO}) <80% of predicted). Overall, the home sleep apnoea test evidenced a moderate elevated AHI of 20.34±13.70 events·h^{-1}, an oxygen desaturation index (ODI) of 10.12±9.05 events·h^{-1} and a nocturnal hypoxaemia of 0.10 min (interquartile range (IQR) 0.00 to 1.00). Sleep apnoea (AHI

Shareable abstract (@ERSpublications)
Sleep disordered breathing may be a risk factor or a sequela of COVID-19. https://bit.ly/37v5Gyz

Cite this article as: Cardoso E, Herrmann MJ, Grize L, *et al*. Is sleep disordered breathing a risk factor for COVID-19 or *vice versa*? *ERJ Open Res* 2022; 8: 00034-2022 [DOI: 10.1183/23120541.00034-2022].

TABLE 1 Characteristics of 58 patients with a history of COVID-19 at admission to hospital and in follow-up with lung function testing and sleep study grouped according to COVID-19 severity

Parameters and measurements	All	Mild/moderate COVID-19	Severe COVID-19	p-value[#]
Subjects, n	58	27	31	
At admission				
Age, years	59.84±13.79	61.11±14.80	58.74±12.98	0.478
Ethnicity				0.843
Caucasian	52 (89.65)	24 (88.89)	28 (90.32)	
Asian	3 (5.17)	2 (7.41)	1 (3.23)	
African	3 (5.17)	1 (3.70)	2 (6.45)	
Male sex	43 (74.13)	18 (66.67)	25 (80.64)	0.247
Smoking status				0.164
Never smoker	30 (51.72)	11 (40.74)	19 (61.29)	
Active smoker	5 (8.62)	4 (14.81)	1 (3.23)	
Former smoker	23 (39.65)	12 (44.44)	11 (35.48)	
Smoking pack-years	25.62±20.85	21.66±19.76	30.58±21.97	0.241
Comorbidities				
Number of comorbidities	3.14±2.17	3.04±2.61	3.23±1.75	0.445
Hypertension	29 (50.00)	14 (51.86)	15 (48.38)	0.999
Chronic kidney disease	14 (24.13)	3 (11.11)	11 (35.48)	**0.037**
Diabetes	13 (22.41)	5 (18.52)	8 (25.80)	0.546
Asthma	8 (13.79)	4 (14.81)	4 (12.90)	1.000
Atrial fibrillation	4 (6.90)	2 (7.41)	2 (6.45)	0.999
COPD	3 (5.17)	2 (7.41)	1 (3.23)	0.593
Coronary heart disease	2 (3.45)	2 (7.41)	0 (0.00)	0.212
Any concomitant medication				
Antihypertensive drugs	30 (51.71)	10 (37.04)	20 (64.51)	0.064
Statins	13 (22.41)	8 (29.62)	5 (16.13)	0.344
Antidiabetic drugs	12 (20.68)	4 (14.81)	8 (25.80)	0.348
Oral anticoagulation	4 (6.90)	1 (3.70)	3 (9.68)	0.620
WHO scale[¶]				**0.003**
3, 4	42 (72.41)	25 (92.59)	17 (54.83)	
5, 6	8 (13.79)	2 (7.41)	6 (19.35)	
7	8 (13.79)	0 (0.00)	8 (25.80)	
Laboratory				
CRP, $mg \cdot L^{-1}$	72.80±65.87	42.16±24.23	97.51±77.93	**0.005**
PCT, $\mu g \cdot L^{-1}$	0.26±0.40	0.19±0.20	0.32±0.50	0.362
Leukocytes, $\times 10^9$ cells$\cdot L^{-1}$	6.12±2.46	5.41±2.70	6.69±2.13	**0.027**
Lymphocytes, $\times 10^9$ cells$\cdot L^{-1}$	0.96±0.51	1.11±0.61	0.83±0.39	**0.043**
D-dimer, $\mu g \cdot mL^{-1}$	1.44±3.08	1.31±1.47	1.54±3.95	0.835
Percentage of radiological findings, %	15.47±11.06	12.03±8.87	18.21±11.99	**0.034**
Length of hospital stay, days	12.70±9.04	7.04±4.60	17.64±9.10	**<0.0001**
Follow-up				
BMI, $kg \cdot m^{-2}$	28.70±5.17	26.74±4.24	30.41±5.36	**0.002**
Pulmonary function test				
TLC, % pred	96.05±10.81	99.07±12.26	93.41±8.74	**0.022**
FVC, % pred	93.31±12.46	94.59±12.16	92.19±12.82	0.271
FEV_1, % pred	92.55±13.99	90.67±15.00	94.19±13.09	0.507
FEV_1/FVC, %	77.18±7.18	74.22±7.92	79.76±5.37	**0.005**
D_{LCO}, % pred	86.09±20.61	82.98±23.36	88.80±17.84	0.533
F_{ENO}, ppb	21.34±18.20	21.88±21.51	20.87±15.08	0.785
P_{aO_2}, mmHg	84.53±12.40	85.43±12.98	83.85±12.10	0.819
P_{aCO_2}, mmHg	36.75±3.95	35.63±3.94	37.65±3.81	0.073
HSAT – WatchPAT200				
ESS	6.07±3.97	6.93±3.58	5.32±4.19	0.089
AHI, $events \cdot h^{-1}$	20.34±13.70	13.13±8.74	26.62±14.24	**0.0001**
ODI, $events \cdot h^{-1}$	10.12±9.05	5.58±4.84	14.08±10.02	**0.0002**
Mean S_{pO_2}, %	94.27±1.47	94.59±1.67	94.00±1.24	0.072
Minimal S_{pO_2}, %	86.39±4.23	87.37±4.54	85.54±3.81	**0.042**
T90%, min, median (IQR)	0.10 (0.00–1.00)	0.00 (0.00–0.5)	0.30 (0.00–1.4)	**0.008**
Mean heart frequency, beats per min	65.08±9.71	65.69±10.06	64.58±9.54	0.810

Continued

TABLE 1 Continued

Parameters and measurements	All	Mild/moderate COVID-19	Severe COVID-19	p-value[#]
TST, min	343.20±93.64	365.60±106.90	323.80±76.83	**0.031**
Sleep efficiency, %	82.45±7.76	82.91±8.34	82.04±7.35	0.469
Light sleep	64.25±9.71	64.80±10.69	63.77±8.93	0.844
Deep sleep	15.03±5.36	15.41±5.78	14.71±5.36	0.588
REM sleep	20.70±6.56	19.78±6.66	21.51±6.49	0.421
Moderate snoring >50 dB, %	4.87±4.44	3.35±3.94	6.09±4.51	**0.005**
OSA				0.087
Present	52 (89.66)	22 (81.48)	30 (96.77)	
Absent	6 (10.34)	5 (18.52)	1 (3.23)	
Severity of OSA				**0.008**
None (AHI <5 events·h^{-1})	6 (10.34)	5 (18.52)	1 (3.23)	
Mild (AHI 5–14 events·h^{-1})	18 (31.03)	12 (44.44)	6 (19.35)	
Moderate (AHI 15–30 events·h^{-1})	22 (37.93)	8 (29.62)	14 (45.16)	
Severe (AHI >30 events·h^{-1})	12 (20.68)	2 (7.41)	10 (32.25)	

Data are presented as n (%) or mean±SD, unless otherwise stated. AHI: apnoea–hypopnoea index; BMI: body mass index; CRP: C-reactive protein; D_{LCO}: diffusing capacity of the lung for carbon monoxide; ESS: Epworth Sleepiness Scale; F_{ENO}: exhaled nitric oxide fraction; FEV_1: forced expiratory volume in 1 s; FEV_1/FVC: Tiffeneau–Pinelli index; FVC: forced vital capacity; HSAT: home sleep apnoea testing; IQR: interquartile range (from first to third quartile); ODI: oxygen desaturation index; OSA: obstructive sleep apnoea; P_{aCO_2}: partial pressure of carbon dioxide; P_{aO_2}: partial pressure of oxygen; PCT: procalcitonin; REM: rapid eye movement; S_{pO_2}: peripheral oxygen saturation; T90%: time with S_{pO_2} under 90%; TLC: total lung capacity; TST: total sleep time; WHO: World Health Organization. [#]: p<0.05 indicates statistically significant differences (indicated in bold). [¶]: WHO clinical improvement scale (draft February 2020): 1–2 ambulatory; 3–4 hospitalised mild disease (3: no oxygen therapy, 4: oxygen by mask or nasal prongs); 5–7 hospitalised severe disease (5: high-flow oxygen or noninvasive ventilation, 6: intubation and mechanical ventilation, 7: ventilation and additional organ support); 8: death.

⩾5 events·h^{-1}) was observed in 52 (89.7%) and clinically symptomatic sleep apnoea (AHI ⩾5 events·h^{-1} plus ESS score ⩾10) in nine of 58 individuals (15.5%).

Body mass index (BMI) differed significantly between the two groups (p=0.002) at follow-up. More patients with a history of severe COVID-19 had sleep apnoea than patients after mild/moderate COVID-19 (97% *versus* 81%, p=0.087). Accordingly, the AHI (26.62±14.24 *versus* 13.13±8.74 events·h^{-1}, p=0.0001) and ODI (14.08±10.02 *versus* 5.58±4.84 events·h^{-1}, p=0.0002) were significantly higher in the group of patients with severe COVID-19. Further, we screened all patients for previous sleep study (n=3) and prior International Classification of Diseases diagnoses for OSA (n=1). Excluding these patients, the association of AHI and COVID-19 severity remained statistically significant (26.63±14.82 *versus* 12.45±8.13 events·h^{-1}, p=0.0001).

A sensitivity analysis adjusted for probable risk factors, including BMI and overall number of comorbidities, confirmed the robustness of the results (adjusting for BMI: mean AHI of 25.92 events·h^{-1} for severe COVID-19 *versus* 14.60 events·h^{-1} for mild/moderate COVID-19, p=0.0027; adjusting for overall number of comorbidities: mean AHI of 25.99 events·h^{-1} for severe COVID-19 *versus* 14.52 events·h^{-1} for mild/moderate COVID-19, p=0.0010). Additional adjustment for age, sex and ethnicity did not change the mean difference between groups, or the statistical significance of the association between AHI and groups.

Patients in the severe COVID-19 group had more moderate (45% *versus* 30%) and severe sleep apnoea (32% *versus* 7.4%) compared with the patients in the mild/moderate COVID-19 group, and nocturnal hypoxaemia was higher in the severe group (median (IQR) 0.30 (0.00–1.40) and 0.00 (0.00–0.50), p=0.008). The associations between CRP at admission, pulmonary function testing parameters (FEV_1 % pred, D_{LCO} % pred and TLC % pred) and AHI were not statistically significant.

OSA is the most prevalent sleep-related breathing disorder. Heinzer *et al*. [2] reported a prevalence of moderate-to-severe sleep apnoea (⩾15 events·h^{-1}) in 49.7% of men and 23.4% of women. The prevalence of sleep apnoea in COVID-19 ranged from 11% to 29% [8]. In our study, moderate-to-severe sleep apnoea was detected in the majority of patients (58.6%) after COVID-19 and was numerically higher in men than in women (63% *versus* 47%, p=0.364). Interestingly, there was a significant difference in the prevalence of moderate-to-severe OSA between the two COVID-19 groups: 37.0% in the mild/moderate COVID-19 group compared to 77.4% in the severe COVID-19 group.

Our findings give room for an association between the severity of the SARS-CoV-2 infection and a higher prevalence and severity of SDB in disease convalescence. To date, there are little data about the prevalence of sleep apnoea after COVID-19. In a previous study, the prevalence of moderate-to-severe sleep apnoea in a nested cohort of patients with acute respiratory distress syndrome (n=34, mean age 51 years, 67.6% male) was significantly higher than in a group with mild/moderate COVID-19 (n=26, mean age 40.4 years, 34.6% male) 3–6 months after discharge (38% *versus* 8%, p<0.01) [9]. The lower prevalence of moderate-severe sleep apnoea (8%) in this mild/moderate COVID-19 group as compared to our study might be explained by the imbalance in gender (fewer men) and the lower age.

On the other side, a higher prevalence of sleep apnoea in almost two-thirds of participants (n=44) was observed during acute SARS-CoV-2 infection in 52% of patients requiring oxygen support and in 48% of patients requiring noninvasive ventilation or invasive ventilation, predicting OSA severity in a previous study [10]. Moreover, a high prevalence of cognitive dysfunction after 6 months (58.4%, 95% confidence interval 56.5% to 60.2%) was reported in a symptomatic-oriented follow-up study of 3762 participants over 7 months [11], presuming an undiagnosed OSA, as neurological impairment has been associated with sleep apnoea [12–15].

OSA with sleep deprivation is associated with a higher susceptibility to viral infections. The dysregulation of the renin–angiotensin system and T-cell production of interleukin-2 promotes increased pro-inflammatory activity, which may play a role in the course of viral pneumonias [16]. Similarly, it is tempting to hypothesise that OSA could lead to a pathophysiological synergic higher level of hypoxaemia, complement activation and a severe cytokine storm during COVID-19 [17].

On the other hand, a possible central nervous system involvement of COVID-19 [18] with impact on chemoreceptors in the lung and lower respiratory airways might represent a risk of developing central sleep apnoea. Rapid eye movement sleep without atonia has been described after acute COVID-19, which might be an early marker of neurodegenerative disease [19]. Furthermore, it would be similarly plausible to consider that underlying pro-inflammatory processes with elevated CRP and interleukin-6 in COVID-19 might lead to a higher incidence of OSA [20]. Additionally, post-intubation granulation tissue formation leading to upper airway narrowing could be a hypothetical explanation favouring OSA [21].

So far, we can neither infer nor refute causality between OSA and COVID-19, as only three individuals of our cohort underwent a sleep study (one of which with no OSA) before the viral disease. Our analysis suggests a relevant association between the severity of SARS-CoV-2 infection and a higher prevalence and severity of sleep apnoea in disease convalescence. Although this is a small, hypothesis-generating study, theoretically, the long-COVID-19 syndrome characterised by excessive sleepiness, fatigue, deterioration of cognitive function, or even depression could also be associated with an undiagnosed novel "COVID-induced sleep apnoea" syndrome with clinical consequences and implications for quality of life. If these findings are to be confirmed, it might be advisable to encourage screening for sleep apnoea in the work-up of long-COVID-19.

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Provenance: Submitted article, peer reviewed.

Conflict of interest: None declared.

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