Early View

Research letter

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

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Take-home message: Sleep-disordered breathing may be a risk factor or a sequela of COVID-19.

ORIGINAL RESEARCH LETTER

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 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 SARS-CoV-2, pulmonary infiltrates on chest-CT-scan and a need for hospitalization due to COVID-19 during the period of 8th March to 1st May 2020 [6]. The absence of a 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 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/min, C-reactive protein levels >75 mg/l, extensive area of ground-glass opacities or progression on computed tomography during hospitalization [6].

Demographic, clinical and outcome data were collected prospectively. Pulmonary function testing including whole-body plethysmography and carbon monoxide diffusion capacity (Vyntus® BODY, Vyair Medical Germany), as well as home sleep apnoea testing (HSAT) with the WatchPAT200 (Itamar Medical Ltd., Caesarea, Israel) were conducted three to twelve months (mean 5.26 ± 3.08 months) after discharge. WatchPAT200 measurements and analyses are standardized, 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 /h), moderate (AHI = 15 - 30/h) and severe (AHI > 30 /h). 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 age of 59.84 ± 13.79 years (mean $\pm$ SD) and mean C-reactive protein (CRP) level of 72.80 ± 65.87 mg/l. 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 the follow-up, six patients (10.3%) presented with obstruction ($FEV_1/FVC < 70\%$), three patients (5.2%) with restriction ($TLC < 80\%$ of predicted), and 20 patients (34.5%) with diffusion impairment ($DLCO < 80\%$ of predicted). Overall, the home sleep apnoea test evidenced a moderate elevated AHI of 20.34 ± 13.70 /h, an oxygen desaturation index (ODI) of 10.12 ± 9.05 /h and a nocturnal hypoxaemia of 0.10 min (0.00 to 1.00). Sleep apnoea ($AHI \geq 5/h$) was observed in 52 (89.7%) and clinically symptomatic sleep apnoea ($AHI \geq 5/h + ESS \text{ score} \geq 10$) in nine of 58 individuals (15.5%).

Body mass index 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% vs 81%, $p=0.008$). Accordingly, the AHI (26.62 ± 14.24 vs 13.13 ± 8.74 /h, $p=0.0001$) and ODI (14.08 ± 10.02 vs 5.58 ± 4.84 /h, $p=0.0002$) were significantly higher in the group of patients with severe COVID-19. Further, we screened all patients for previous study sleep ($n=3$) and prior ICD diagnoses for OSA ($n=1$). Excluding these patients, the association of AHI and COVID-19 severity remained statistically significant (26.63 ± 14.82 vs 12.45 ± 8.13 /h, $p=0.0001$).

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 /h for severe COVID-19 vs 14.60 /h for mild/moderate COVID-19, $p=0.0027$; adjusting for overall number of comorbidities - mean AHI of 25.99 /h for severe COVID-19 vs 14.52 /h for mild/moderate COVID-

19, $p=0.0010$). Additional adjustment for age, sex and ethnicity did not change the mean difference between groups, neither the statistical significance of the association between AHI and groups.

Patients in the severe COVID-19 group had more moderate (45% vs 30%) and severe sleep apnoea (32% vs 7.4%) compared to the patients in the mild/moderate COVID-19 group, and nocturnal hypoxaemia was higher in 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, PFT parameters (FEV1, % pred, DLCO, % pred and TLC, % pred) and AHI were not statistically significant.

OSA is the most prevalent sleep-related breathing disorder. Heinzer et al. reported a prevalence of moderate-to-severe sleep apnoea (≥ 15 events/h) in 49.7% men and 23.4% women [2]. 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 ARDS ($n=34$, mean age 51, male 67.6%) was significantly higher than in a group with mild/moderate COVID-19 ($n=26$, mean age 40.4 years, male 34.6) 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 2/3 of participants ($n=44$) was observed during acute SARS-CoV-2 infection in 52 % patients requiring oxygen support and in 48% patients requiring NIV or invasive ventilation, predicting OSA severity in a previous study [10]. Moreover, a high prevalence of cognitive dysfunction after 6 months (58.4%, 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, once neurological impairment have 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 hypothesize that OSA could lead to a pathophysiological synergic higher level of hypoxemia, 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 (REM) 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, a post-intubation granulation tissue formation leading to upper airway narrowing could be a hypothetical explanation favoring 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 on quality-of-life. If these findings are to be confirmed, it might be advisable to encourage the screening for sleep apnoea in the work-up of long-COVID-19.

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 (n = 58)	Mild/moderate COVID-19 (n = 27)	Severe COVID-19 (n = 31)	p‡
At admission:				
Age, years	59.84 ± 13.79	61.11 ± 14.80	58.74 ± 12.98	0.478
Ethnicity				
Caucasian	52 (89.65)	24 (88.89)	28 (90.32)	0.843
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				
Never smoker	30 (51.72)	11 (40.74)	19 (61.29)	0.164
Active smoker	5 (8.62)	4 (14.81)	1 (3.23)	
Former smoker	23 (39.65)	12 (44.44)	11 (35.48)	
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 (18.51)	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 (10.37)	20 (64.51)	0.064
Statins	13 (22.41)	8 (29.62)	5 (16.12)	0.344
Antidiabetic drugs	12 (20.68)	4 (14.81)	8 (25.80)	0.348
Oral anticoagulation	4 (7.14)	1 (4.00)	3 (9.68)	0.620
WHO scale				
3, 4	42 (72.41)	25 (92.59)	17 (54.83)	0.003
5, 6	8 (13.79)	2 (7.41)	6 (19.35)	
7	8 (13.79)	0 (0.00)	8 (25.80)	
Laboratory				
CRP, mg/l	72.80 ± 65.87	42.16 ± 24.23	97.51 ± 77.93	0.005
PCT, µg/l	0.26 ± 0.40	0.19 ± 0.20	0.32 ± 0.50	0.362
Leukocytes, x10S9/l	6.12 ± 2.46	5.41 ± 2.70	6.69 ± 2.13	0.027
Lymphocytes, x10S9/l	0.96 ± 0.51	1.11 ± 0.61	0.83 ± 0.39	0.043
D-Dimer, µg/ml	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/m²	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
DLCO, % pred	86.09 ± 20.61	82.98 ± 23.36	88.80 ± 17.84	0.533
FeNO, ppb	21.34 ± 18.20	21.88 ± 21.51	20.87 ± 15.08	0.785
PaO ₂ , mmHg	84.53 ± 12.40	85.43 ± 12.98	83.85 ± 12.10	0.819
PaCO ₂ , mmHg	36.75 ± 3.95	35.63 ± 3.94	37.65 ± 3.81	0.073
HSAT – WatchPAT200				
Epworth Sleepiness Score	6.07 ± 3.97	6.93 ± 3.58	5.32 ± 4.19	0.089
Apnoea-hypopnea index, /h	20.34 ± 13.70	13.13 ± 8.74	26.62 ± 14.24	0.0001
Oxygen desaturation index, /h	10.12 ± 9.05	5.58 ± 4.84	14.08 ± 10.02	0.0002
Mean SpO ₂ , %	94.27 ± 1.47	94.59 ± 1.67	94.00 ± 1.24	0.072
Minimal SpO ₂ , %	86.39 ± 4.23	87.37 ± 4.54	85.54 ± 3.81	0.042
T90%: Time with SpO ₂ under 90%, min*	0.10 (0.00 to 1.00)	0.00 (0.00 to 0.5)	0.30 (0.00 to 1.4)	0.008
Mean heart frequency, bpm	65.08 ± 9.71	65.69 ± 10.06	64.58 ± 9.54	0.810
Total sleep time, 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	0.8437
Deep Sleep	15.03 ± 5.36	15.41 ± 5.78	14.71 ± 5.36	0.5877
REM Sleep	20.70 ± 6.56	19.78 ± 6.66	21.51 ± 6.49	0.4208
Moderate snoring > 50dB, %	4.87 ± 4.44	3.35 ± 3.94	6.09 ± 4.51	0.0051
OSA				
Present	52 (89.66)	22 (81.48)	30 (96.77)	0.087
Absent	6 (10.34)	5 (18.52)	1 (3.22)	
Severity of OSA				
None (AHI <5)	6 (10.34)	5 (18.51)	1 (3.23)	0.008
Mild (AHI = 5 - 14)	18 (31.03)	12 (44.44)	6 (19.35)	
Moderate (AHI = 15 - 30)	22 (37.93)	8 (29.62)	14 (45.16)	
Severe (AHI > 30)	12 (20.68)	2 (7.407)	10 (32.25)	

*Median (IQR) IQR=interquartile range (from first to third quartile)

Legend: numbers are absolute counts (%) or means (SD); AHI: Apnoea–hypopnea index; BMI: Body mass index; COPD: chronic obstructive pulmonary disease; DLCO: Diffusing capacity for carbon monoxide; FeNO: Exhaled nitric oxide; FEV₁: Forced expiratory volume in 1 second; FEV₁/FVC: Tiffeneau-Pinelli index; FVC: Forced vital capacity; PaCO₂: partial pressure of carbon dioxide; PaO₂: Partial pressure of oxygen, PCT: Procalcitonin; SD: Standard deviation; SpO₂: peripheral Oxygen saturation; TLC: Total lung capacity; TST: Total sleep time; WHO scale (WHO clinical improvement scale – draft Feb 2020): 1-2 ambulatory, 3-4 hospitalized mild disease (3: no oxygen therapy, 4:

oxygen by mask or nasal prongs), 5-7 hosp. severe disease (5: high-flow oxygen or non-invasive ventilation, 6: intubation and mechanical ventilation, 7: ventilation and additional organ support), 8-death.

Abbreviation list:

Chest-CT-scan: chest computed tomography scan; CRP: c-reactive protein; DLCO: Diffusing capacity for carbon monoxide; IL-6: Interleukin 6; mg/dL: milligrammes per deciliter; mg/l: milligrammes per litre; PCR test: Polymerase chain reaction test

References

1. Dimitrov S, Lange T, Gouttefangeas C, Jensen ATR, Szczepanski M, Lehnholz J, Soekadar S, Rammensee HG, Born J, Besedovsky L: **Gα(s)-coupled receptor signaling and sleep regulate integrin activation of human antigen-specific T cells.** *J Exp Med* 2019, **216**:517-526.
2. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, Mooser V, Preisig M, Malhotra A, Waeber G, et al: **Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study.** *Lancet Respir Med* 2015, **3**:310-318.
3. Cade BE, Dashti HS, Hassan SM, Redline S, Karlson EW: **Sleep Apnea and COVID-19 Mortality and Hospitalization.** *Am J Respir Crit Care Med* 2020, **202**:1462-1464.
4. Goldstein CA, Rizvydeen M, Conroy DA, O'Brien LM, Gupta G, Somers EC, Sharma P, Golob JL, Troost JP, Burgess HJ: **The prevalence and impact of pre-existing sleep disorder diagnoses and objective sleep parameters in patients hospitalized for COVID-19.** *J Clin Sleep Med* 2021, **17**:1039-1050.
5. Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, Amadou C, Arnault G, Baudoux F, Bauduceau B, et al: **Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study.** *Diabetologia* 2020, **63**:1500-1515.
6. Sava M, Sommer G, Daikeler T, Woischnig AK, Martinez AE, Leuzinger K, Hirsch H, Erlanger T, Wiencierz A, Bassetti S, et al: **Ninety-day outcome of patients with severe COVID-19 treated with tocilizumab - a single centre cohort study.** *Swiss Med Wkly* 2021, **151**:w20550.
7. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, Harrod CG: **Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline.** *J Clin Sleep Med* 2017, **13**:479-504.
8. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, Greninger AL, Pipavath S, Wurfel MM, Evans L, et al: **Covid-19 in Critically Ill Patients in the Seattle Region - Case Series.** *N Engl J Med* 2020, **382**:2012-2022.
9. Labarca G, Henriquez-Beltran M, Llerena F, Erices G, Lastra J, Enos D, Castillo D, Fraga M, Lamperti L, Ormazabal V, et al: **Undiagnosed sleep disorder breathing as a risk factor for critical COVID-19 and pulmonary consequences at the midterm follow-up.** *Sleep Med* 2021.
10. Perger E, Soranna D, Pengo M, Meriggi P, Lombardi C, Parati G: **Sleep-disordered Breathing among Hospitalized Patients with COVID-19.** *Am J Respir Crit Care Med* 2021, **203**(2):239-241.
11. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, Redfield S, Austin JP, Akrami A: **Characterizing long COVID in an international cohort: 7 months of symptoms and their impact.** *E Clinical Medicine* 2021, **38**:101019.
12. Vanek J, Prasko J, Genzor S, Ociskova M, Kantor K, Holubova M, Slepecky M, Nesnidal V, Kolek A, Sova M: **Obstructive sleep apnea, depression and cognitive impairment.** *Sleep Med* 2020, **72**:50-58.
13. Dzierzewski JM, Dautovich N, Ravyts S: **Sleep and Cognition in Older Adults.** *Sleep Med Clin* 2018, **13**:93-106.
14. Liu X, Ma Y, Ouyang R, Zeng Z, Zhan Z, Lu H, Cui Y, Dai Z, Luo L, He C, Li H, Zong D, Chen Y: **The relationship between inflammation and neurocognitive dysfunction in obstructive sleep apnea syndrome.** *J Neuroinflammation* 2020, **17**:229.
15. Kerner NA, Roose SP: **Obstructive Sleep Apnea is Linked to Depression and Cognitive Impairment: Evidence and Potential Mechanisms.** *Am J Geriatr Psychiatry* 2016, **24**:496-508.
16. Prather AA, Janicki-Deverts D, Hall MH, Cohen S: **Behaviorally Assessed Sleep and Susceptibility to the Common Cold.** *Sleep* 2015, **38**:1353-1359.
17. McSharry D, Malhotra A: **Potential influences of obstructive sleep apnea and obesity on COVID-19 severity.** *J Clin Sleep Med* 2020, **16**:1645.
18. Saleki K, Banazadeh M, Saghaizadeh A, Rezaei N: **The involvement of the central nervous system in patients with COVID-19.** *Rev Neurosci* 2020, **31**:453-456.

19. Heidbreder A, Sonnweber T, Stefani A, Ibrahim A, Cesari M, Bergmann M, Brandauer E, Tancevski I, Löffler-Ragg J, Högl B: **Video-polysomnographic findings after acute COVID-19: REM sleep without atonia as sign of CNS pathology?** *Sleep Med* 2021, **80**:92-95.
20. Kritikou I, Basta M, Vgontzas AN, Pejovic S, Liao D, Tsaoussoglou M, Bixler EO, Stefanakis Z, Chrousos GP: **Sleep apnoea, sleepiness, inflammation and insulin resistance in middle-aged males and females.** *Eur Respir J* 2014, **43**:145-155.
21. Shinn JR, Kimura KS, Campbell BR, Sun Lowery A, Wootten CT, Garrett CG, Francis DO, Hillel AT, Du L, Casey JD, et al: **Incidence and Outcomes of Acute Laryngeal Injury After Prolonged Mechanical Ventilation.** *Crit Care Med* 2019, **47**:1699-1706.