Sleep Disordered Breathing Among Hospitalized Patients due to COVID-19

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To the editor:

Coronavirus disease 2019 (COVID-19) has severely affected healthcare systems all over the world. Although age, hypertension, cardiovascular diseases, lung diseases and diabetes mellitus seem to represent the main risk factors for worse outcome in COVID-19 (1), a possible role has also been ascribed to sleep disordered breathing (SDB) (2-4). A recent preliminary study collecting questionnaire data in a case series of COVID-19 pneumonia showed that 25% of patients presented a history of SDB (5). It has been hypothesized that SDB might predispose to COVID-19 severe pneumonia, and that the coexistence of these two respiratory conditions might worsen patients' prognosis (2, 4).

In those days of pandemic outbreak, we sought to correlate the presence and severity of SDB with COVID-19 outcomes during hospitalization. Despite the dramatic situation we were experiencing, which prevented us from optimizing the standardization of exams, such as sleep apnea test (SAT), we managed to include patients during spontaneous breathing for SDB evaluation.

Consecutive patients, hospitalized at our Institution in Milan due to COVID-19 over one month from April 8th to May 8th underwent a SAT. The test was performed either at entry, or at any time during the course of hospitalization, provided that the patients was breathing spontaneously. Those who had previously required ventilatory support due to COVID-19 respiratory failure underwent a SAT only after weaning from either non-invasive (NIV) or invasive mechanical ventilation after improvement of their clinical conditions within the recruitment period. Outcomes were evaluated at the time of patients' discharge and defined according to the two types of treatments needed during hospitalization: 1) none or oxygen

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support, or 2) ventilation with NIV, including continuous or bilevel positive airways pressure, or with mechanical ventilation in the intensive care unit (ICU). Due to the severity of COVID-19 disease, many hospitalized patients required NIV or mechanical support since the time of admission and for a long time, or eventually died, so that they could not be included in our study. SAT were then scored after the recruitment period by a sleep clinician blinded to hospitalization outcomes. Patients were treated according to their clinical conditions and following the local guidelines for COVID-19. Based on the international criteria and apnea-hypopnea index (AHI) calculation, we defined the disease as: 1) "none" if AHI < 5/h; 2) "mild" if 5 ≤ AHI < 15; 3) "moderate-to-severe" if 15 ≤ AHI < 30/h; 4) "severe" if AHI ≥ 30/h.

The 95% confidence interval (95% CI) of SDB presence was calculated through the exact Clopper-Pearson method. Poisson regression model with robust error variance was implemented to estimate the prevalence ratio and its 95% CI to receive mechanical or non-mechanical ventilation. The model included as covariates gender, age and BMI (body mass index) as continuous variables and those variables that presented a p-value ≤0.15 in the univariate analysis.

Our study received ethical clearance from the appropriate authority and all patients provided informed consent to the collection of their clinical data and to the execution of sleep tests for research purposes.

Our screened sample included 93 subjects. Among them, 39 did not perform SAT as they were using 24 h NIV due to COVID-19-related respiratory failure. Out of total 44 patients who underwent SAT, 13 were on oxygen treatment. 2 subjects were treated with

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nocturnal continuous positive airway pressure (CPAP) due to their previous history of obstructive sleep apnea (OSA) and were included in the study.

The proportion of SDB presence in our sample was 75% (95% CI: 60% - 87%).

Table 1 describes the main characteristics of the 44 subjects stratified for SDB severity: 33 patients (75%) had SDB, of which 15 (34%) presented mild SDB, 6 (14%) moderate SDB and 12 (27%) a severe disease. Moreover, 15 (34%) patients showed OSA and 18 (41%) central sleep apnea (CSA). Of the 8 patients who had Cheyne-Stokes respiration with central sleep apnea (CSR-CSA) breathing, 1 had a history of stroke, 1 of renal failure, 3 of chronic ischemic cardiopathy and 3 were in atrial fibrillation.

Concerning outcomes, 24 patients (52%) necessitated only oxygen support, while 22 (48%) needed NIV or invasive ventilation in the ICU. Ventilated patients were characterized by higher BMI, predominant OSA and greater obstructive AHI, as shown in Table 2. SpO_2 parameters did not differ between the groups, feasibly because of the required oxygen support in the COVID-19 unit. Multivariate analysis revealed that higher BMI (prevalence ratio [PR] 1.20; CI 1.10-1.31; $p<0.001$) and higher obstructive AHI (PR 1.03; CI 1.01-1.05; $p=0.015$) were the variables significantly associated with the need of ventilation.

To our knowledge, this is the first evaluation of SAT in hospitalized COVID-19 patients. Almost two thirds of our sample had SDB, and OSA severity predicted respiratory outcome. Several mechanisms may contribute to the increased risk of severe COVID-19 in OSA patients (6). Even though obesity confirms an established relation with OSA (4), our findings highlight that higher obstructive AHI is also associated with need of non-invasive or invasive ventilation, even after controlling for age and BMI.

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Our interpretation is supported by the results of a recent study by Feuth and colleagues who found that 29% of their cohort of patients hospitalized for COVID-19 presented a previous diagnosis of OSA, although not confirmed using SAT (7). Previous evidence on hospitalized patients for different kinds of respiratory infections has shown worse outcomes in subjects with a history of OSA compared with those without OSA (8).

Systemic inflammation is a pathophysiologic feature shared by both COVID-19 and OSA. OSA-related intermittent hypoxia and fragmented sleep determine a pro-inflammatory status that may enhance the typical COVID-19 cytokine storm, thus worsening disease evolution.

As major limitation of our study, we have to specify that the emergency conditions in which we were operating prevented us from evaluating a higher number of patients for SDB, and from including more subjects characterized by adverse outcomes. Moreover, the design of our study does not allow to conclude for a causal link between OSA and COVID-19 severity nor to define the direction of such a link. This is because of the different time points at which SAT was performed in different subjects, because of the observational nature of our study and due to the lack of comparison with a control group. In spite of these limitations, however, our study offers for the first time information on the prevalence of OSA in COVID-19 patients by means of a proper objective testing.

This high rate of underdiagnosed SDB, in particular OSA, might act as cofactor in the elevated susceptibility for worse COVID-19 sequelae, independently of BMI. An appropriate assessment of SDB presence, type and severity in COVID-19 patients, also in the hospital setting, might thus favor a more accurate risk stratification and also help decision-making in therapeutic interventions (9, 10). The possible role of SDB treatment in prognosis improvement

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of hospitalized patients for COVID-19 disease needs to be further investigated through properly sized intervention studies.

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Table 1: Baseline characteristics of our subjects classified by sleep apnea severity.

	AHI < 5 N = 11 (25%)	5 ≤ AHI < 15 N = 15 (34%)	15 ≤ AHI < 30 N = 6 (14%)	AHI ≥ 30 N = 12 (27%)
Age, yrs	51 ± 16	62 ± 17	70 ± 11	72 ± 14
Gender, female	6 (55%)	4 (27%)	2 (33%)	3 (25%)
BMI, kg/m^2	27 [24-28]	25 [23-30]	29 [27-30]	24 [22-26]
AHI,	1 [0-2]	8 [7-10]	24 [20-27]	49 [37-56]
AHI in the supine position,	1 [0-2]	10 [7-12]	27 [22-30]	50 [40-56]
AHI non-supine,	1 [0-1]	5 [0-6]	2 [0-18]	26 [0-60]
Apnea index,	1 [0-1]	3 [1-4]	15 [10-22]	17 [8-41]
Hypopnea index,	1 [0-1]	6 [3-8]	8 [4-12]	23 [12-33]
AHI Obstructive,	0 [0-1]	3 [2-5]	22 [19-25]	1 [0-3]
AHI Central,	1 [0-1]	5 [3-7]	2 [1-3]	43 [28-56]
CSR-CSA,	0	0	0	8 (67%)
Time spent in supine position, min	299 [174-498]	320 [183 - 536]	420 [348-493]	484 [271-540]
Average SpO_2 during the night, %	96 [94-97]	95 [94-96]	93 [91-95]	94 [91-95]
SpO_2 Nadir, %	88 [85-92]	85 [81-87]	85 [73-89]	82 [73-88]
ODI,	2 [1-3]	10 [7-13]	25 [22-27]	43 [33-35]
Time spent with SpO_2 below 90%, min	0 [0-1]	0 [0-1]	1 [0-20]	3 [0-35]
Smoking				
Active	0	0	1 (17%)	2 (17%)
Former	0	4 (27%)	1 (17%)	3 (25%)
Never	11 (100%)	11 (73%)	4 (6%)	7 (58%)
Hypertension	1 (9%)	9 (60%)	5 (93%)	5 (42%)
Dyslipidemia	0	2 (13%)	0	0
Atrial Fibrillation	0	2 (13%)	1 (17%)	3 (25%)
Stroke	1 (9%)	0	0	1 (8%)
CIC	1 (9%)	1 (5%)	0	4 (33%)
Heart failure	0	0	0	1 (8%)
Renal failure	0	0	0	2 (17%)
Diabetes	0	1 (5%)	0	0
COPD	0	1 (5%)	2 (33%)	2 (17%)
Asthma	1 (9%)	0	0	0

Data are expressed as mean ± SD or number (percentage) or median [interquartile range].

Definition of abbreviations: BMI = body max index; AHI = apnea-hypopnea index; CSR-CSA = Cheyne-Stokes Respiration; SpO_2 = arterial oxygen saturation; ODI = oxygen desaturation index; CIC = chronic ischemic heart disease; COPD = chronic obstructive pulmonary disease.

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Table 2. Univariate analyses of factors associated with no need or with need of non-invasive or invasive ventilation.

46 patients	No or Oxygen N=24	Pulmonary Ventilation N=22	p
Age, yrs	63 ±18	65 ± 15	0.67
Gender, female	8 (33%)	6 (27%)	0.65
BMI, kg/m^2	24.3 ± 3.3	28.4 ± 4.2	**<0.01**
AHI,	9 [2-28]	20 [7-30]	0.26
AHI central,	5 [1-22]	5 [1-12]	0.87
AHI obstructive,	1 [0-3]	4 [1-20]	**0.03**
SDB type			**<0.01**
No	7 (29%)	4 (18%)	
OSA	3 (13%)	14 (64%)	
CSA	12 (50%)	6 (27%)	
ODI,	17 ± 18	21±18	0.49
Mean SpO_2, %	95 [94-96]	94 [92-96]	0.48
Lowest SpO_2, %	85 [80-90]	85 [73-89]	0.66
SpO_2 < 90%, min	0 [0-3]	1 [0-8]	0.41
Smoking			0.97
Active	2 (8%)	1 (5%)	
Former	3 (13%)	4 (18%)	
Never	19 (79%)	17 (77%)	
Comorbidities	17 (70%)	13 (59%)	0.19
Hypertension	9 (38%)	13 (59%)	0.10
Dyslipidemia	2 (8%)	1 (5%)	0.99

Data are expressed as mean ± SD or number (percentage) or median [interquartile range]. Comorbidities included history of at least one of the following: atrial fibrillation, stroke, chronic ischemic heart disease, heart failure, renal failure, diabetes, chronic obstructive pulmonary disease, asthma.

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