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High-risk obstructive sleep apnea is related to longer hospital stay in COVID-19 patients

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Abstract:

BACKGROUND AND AIM: Obstructive sleep apnea (OSA), having an increased inflammatory state due to an imbalance between sympathetic and parasympathetic activity, intermittent hypoxia, and increased cytokines, may aggravate the immune response for COVID-19 infection. Our aim was to evaluate the effect of OSA upon inflammatory response and length of stay in patients with favorable outcomes.

METHODS: Patients admitted to an outpatient clinic after being hospitalized for treatment of COVID-19 were included consecutively in this cross-sectional multicenter observational study. STOP-Bang Questionnaire and a cut-off value of 3 points were used to identify patients with a high risk of OSA.

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RESULTS: Study population consisted of 201 patients with a median STOP-Bang score of 2.0 (1.0–4.0) points. According to the cut-off value of 3 points, 94 (46.8%) patients were classified as high-risk OSA patients. High-risk OSA patients were older, had many comorbidities such as hypertension, coronary artery disease, and diabetes mellitus, had higher serum D-dimer, ferritin, C-reactive protein, and procalcitonin measurements, and had a longer hospital stay. Possible risk factors associated with length of stay were age, lymphocyte count, and total STOP-Bang score. Multivariable analysis revealed that a 1 point increase in STOP-Bang score results in a 0.43 day longer hospital stay.

CONCLUSIONS: Prevalence of OSA within COVID-19 patients with favorable outcomes is similar to the general population. However, the length of stay is related to the presence of high-risk OSA. Our study, therefore, suggests that OSA is related to delayed improvement of COVID-19 infection.

Keywords:

COVID-19, length of stay, obstructive sleep apnea, STOP-Bang Questionnaire

Introduction

Obstructive sleep apnea (OSA) results in immune dysregulation and therefore is related to greater severity of infections and higher cancer incidence.[1] Present studies demonstrated changes in natural killer (NK), cytotoxic T cells, and regulatory T cells[2,3] in peripheral blood samples. Reduction of $CD19^+$ B cells, $CD3^+/CD4^+$ T cell ratio, and $CD4^+/CD8^+$ T cell ratio is correlated with apnea-hypopnea index (AHI) and oxygen desaturation.[2] OSA has an NK suppressing effect by increasing TGF-β release.[4] In addition to cellular effects, OSA has a direct effect on oxidative imbalance and inflammatory cascade activation via intermittent hypoxia.[5] Aggravated alveolar macrophage dysfunction due to decreased PPAR-γ functional activity in OSA patients increases pulmonary disease susceptibility.[6] OSA patients have significantly increased mortality risk in face of sepsis compared with matched controls.[7]

An exacerbated inflammatory response is one of the key reasons for severe COVID-19 to progress to acute respiratory distress. It can be hypothesized that OSA, having an increased inflammatory state due to an imbalance between sympathetic and parasympathetic activity, intermittent hypoxia, and increased cytokines, may aggravate the immune response for COVID-19 infection.[8]

Risk factors for infection, mortality, and adverse outcomes for COVID-19 patients have been identified in various studies. Some studies identified having OSA as a significantly increased risk for COVID-19 infection.[9] OSA is also related to increased risk for hospitalization and respiratory failure independent of diabetes mellitus (DM), hypertension (HT), and body mass index (BMI).[9,10]

The role of OSA on mortality and adverse conditions among patients with COVID-19, who were treated in hospital and intensive care unit (ICU) settings, was evaluated in previous studies.[11–14] The aim of this study was to evaluate the occurrence of OSA and its effect on inflammatory response and length of stay in patients with favorable outcomes.

Materials and Methods

Data collection and definitions

The study was designed as a multicenter study. The centers included were: one university hospital, six state hospitals, and two private hospitals. Every researcher included at least 20 patients to ensure generalizability.

Patients admitted to an outpatient clinic after being hospitalized for treatment for COVID-19 between June 1 and July 31, 2020, were included consecutively in this cross-sectional multicenter observational study. Patients who had an ICU admission and had an inability to answer the questionnaire were excluded from the study. Proven COVID-19 is defined as patients with positive real-time reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2. Demographic data, clinical presentation, laboratory tests, and chest CT data were collected from inpatient medical records by a trained team of pulmonary physicians. Laboratory data included complete blood count, infection biomarkers, coagulation profile, and serum ferritin measured upon hospital admission.

Clinical decisions such as hospital admission and treatment were in accordance with national guidelines conducted by the Turkish Ministry of Health and therefore standardized for all patients.[15] COVID-19 patients with mild disease are isolated and treated at home. Patients with respiratory rate >30 min^{-1}, oxygen saturation

≤90%, age > 50 years, lymphocyte count <800 μL^{-1}, C-reactive protein (CRP) >50 mg/L, ferritin >500 ng/mL, or D-dimer >1000 ng/mL and with bilateral infiltration in Chest CT are considered to be treated in a hospital. Favipiravir (1600 mg twice daily as a loading dose followed by 600 mg twice daily as a maintenance dose) is the main treatment option in stable patients. Immune plasma treatment, systemic methylprednisolone (0.5–1 mg/kg), and tocilizumab (8 mg/kg) were considered in patients with clinical worsening according to national guidelines.

Questionnaire

STOP-Bang questionnaire is an 8-item questionnaire developed by Acar et al. validated in Turkish.[16,17] STOP-Bang is a validated screening tool for OSA in different populations.[18] Each item is scored as 1 point, and patients with higher scores have a higher probability of OSA.[19] A recent meta-analysis demonstrated that a cut-off value of 3 points is a valid tool to detect OSA in the general population with high sensitivity and negative predictive value.[20] In this study, 3 points was used as a cut-off value for defining patients with a high risk of OSA.

Statistical analysis

The data were analyzed using Statistical Package for Social Sciences (SPPS) version 22. The variables were analyzed for normal distribution using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test). Normally distributed continuous data were presented as means and standard deviations, while nonnormally distributed continuous data were presented as medians and interquartile ranges (IQR). Comparison of two groups with normally and nonnormally distributed data were analyzed by Student's t-test and Mann–Whitney U test, respectively. The Chi-squared test was used for the comparison of categorical variables, which were presented as observation counts and percentages. Candidate risk factors related to the length of hospitalization were evaluated first by univariate analysis and then possible risk factors with p values below 0.10 were evaluated by a multiple linear regression model to identify independent predictors of length of stay. Values of $p<0.05$ were considered statistically significant.

The study was approved by the ethics committee of the Uludağ University. Written informed consent was obtained from all participants prior to their inclusion in the study.

Table 1: Population characteristics

Variables	(n=201)
Age (years)	49.4±16.5
Male gender, n (%)	117 (58.2)
Smoking status, n (%)	
Current smokers	25 (12.4)
Ex-smokers	52 (25.9)
Coexisting conditions	
HT, n (%)	56 (27.9)
DM, n (%)	34 (16.9)
Coronary artery disease, n (%)	13 (6.5)
COPD, n (%)	7 (3.5)
Asthma, n (%)	22 (10.9)
OSA, n (%)	4 (2.0)
Leukocyte count (K/μL)	6020 (4800–7530)
Lymphocyte count (K/μL)	1520 (1100–2020)
D-dimer (mg/L)	0.46 (0.25–2.30)
Ferritin (μg/L)	124.0 (50.0–298.8)
CRP (mg/L)	6.4 (2.2–29.6)
Procalcitonin (μg/L)	0.03 (0.02–0.05)
STOP-Bang score, n (%)	2.0 (1.0–4.0)
Snoring	87 (43.3)
Tiredness	57 (28.4)
Observed apnea	20.0 (10.0)
Length of stay (days)	10.0±4.5

Data are shown as mean±standard deviation or median (IQR 25–75), as appropriate. HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, OSA: Obstructive sleep apne, CRP: C-reactive protein

Results

A total of 331 patients were evaluated in an outpatient clinic after discharge from pandemic clinics. After excluding RT-PCR negative patients, 201 patients with a mean age of 49.4±16.5 years were included in the study. Male patients constituted 58.2% of the study population, and the most frequent coexisting conditions were HT, DM, and asthma. Population characteristics are presented in Table 1. Median STOP-Bang score for the study population was 2.0 (1.0–4.0). According to a cut-off value of 3 points, 107 (53.2%) patients were classified as low-risk and 94 (46.8%) as high-risk OSA patients. On the other hand, according to a cut-off value of 4 points, 148 (73.6%) patients were classified as low-risk OSA while 53 (26.4%) patients were classified as high-risk OSA. Comparison of patients grouped according to STOP-Bang score revealed that high-risk OSA patients were older, had many comorbidities such as HT, coronary artery disease, and DM, had higher serum D-dimer, ferritin, CRP, procalcitonin measurements, and longer hospital stay (Table 2).

Table 2: Comparison of patients grouped according to STOP-Bang score

Variables	STOP-Bang score <3 (n=107)	STOP-Bang score ≥3 (n=94)	p	STOP-Bang score <4 (n=148)	STOP-Bang score ≥4 (n=53)	p
Age (years)	42.1±13.9	57.6±15.4	<0.001	44.9±14.0	61.8±14.1	<0.001
Male gender, n (%)	58 (54.2)	59 (62.7)	0.25	82 (55.4)	35 (66.0)	0.19
Smoking status, n (%)						
Current smokers	17 (15.8)	8 (8.5)	0.09	23 (15.5)	2 (3.7)	0.05
Ex-smokers	21 (19.6)	33 (35.1)		31 (20.9)	21 (39.6)	
Coexisting conditions	39 (36.4)	72 (62.7)	<0.001	63 (42.5)	48 (90.5)	<0.001
HT, n (%)	11 (10.2)	45 (47.8)	<0.001	22 (14.8)	34 (64.1)	<0.001
DM, n (%)	7 (6.5)	27 (28.7)	<0.001	20 (13.5)	14 (26.4)	0.05
CAD, n (%)	2 (1.8)	11 (11.7)	0.007	7 (4.7)	6 (11.3)	0.11
COPD, n (%)	4 (3.7)	3 (3.1)	1	4 (2.7)	3 (5.6)	0.38
Asthma, n (%)	9 (8.4)	13 (1.8)	0.26	12 (8.1)	10 (18.8)	0.04
Leukocyte count (K/μL)	5950 (4815–7780)	6060 (4800–7450)	0.91	5920 (4800–7770)	6350 (5200–7440)	0.47
Lymphocyte count (K/μL)	1700 (1135–2180)	1420 (1040–1840)	0.08	1600 (1190–2070)	1340 (970–1990)	0.08
D-dimer (mg/L)	0.45 (0.19–2.1)	0.48 (0.30–0.99)	0.58	0.3 (0.2–6.7)	0.5 (0.3–1.1)	0.07
Ferritin (μg/L)	102.0 (43.7–207.0)	175.0 (65.4–365.6)	0.005	119.0 (45.1–240.5)	192.0 (74.1–361.6)	0.01
CRP (mg/L)	4.5 (1.3–16.9)	11.6 (3.1–42.9)	<0.001	4.8 (1.6–16.8)	23.0 (5.8–60.4)	<0.001
Procalcitonin (μg/L)	0.02 (0.02–0.03)	0.04 (0.02–0.08)	0.05	0.02 (0.02–0.04)	0.06 (0.03–0.08)	0.01
STOP-Bang score						
Snoring, n (%)	19 (17.7)	68 (72.3)	<0.001	46 (31.0)	41 (77.3)	<0.001
Tiredness, n (%)	11 (10.2)	46 (48.9)	<0.001	25 (16.8)	32 (60.3)	<0.001
Observed apnea, n (%)	0 (0.0)	20 (21.2)	<0.001	3 (2.0)	17 (32.0)	<0001
Length of stay (days)	9.1±4.2	11.0±4.6	0.02	9.2±4.1	11.7±5.0	0.01

Data are shown as mean±standard deviation or median (IQR 25–75), as appropriate. HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein

Possible risk factors associated with length of stay were age, lymphocyte count, and total STOP-Bang score. Multivariable analysis revealed that a 1 point increase in STOP-Bang score results in a 0.43 day longer hospital stay, and a decrease of 100 K/μL in lymphocyte count results in a 0.1 day increase in the length of stay (Table 3). R2 for this regression model was 0.087.

Discussion

In our study, 46.8% of the patients were classified as high-risk OSA. A general population study conducted in Cyprus, using STOP-Bang questionnaire, revealed that 35.9% of the population had ≥3 points.[21] Meta-analysis of five studies evaluating the general population found that the prevalence of all OSA (AHI ≥5) to be 57.6% and moderate-severe OSA (AHI >15) to be 21.3%.[20] These studies indicate a similar frequency of OSA in hospitalized than discharged COVID-19 patients compared with the general population. However, Miller et al.[22] noted in their systematic review that the prevalence of OSA among COVID-19 patients was 6.3%–28%. This difference might be due to underdiagnoses of OSA. OSA is underdiagnosed in the general population and especially among hospitalized patients.[23] Previous studies indicated a prevalence of undiagnosed OSA among cardiac inpatients as 48%,[24] among clinically deteriorating patients as 37.8%,[23] among surgery patients as 82%,[25] and among COPD patients as 46%.[26] Undiagnosed OSA is found to be related to ICU admission, respiratory complications, and mortality.[24–26]

Our study revealed that being in the high-risk OSA group is independently related to the hospital length of stay. Peker et al.[27] used Berlin Questionnaire to group patients as low- and high-risk for OSA and revealed that high-risk OSA patients required ICU treatment and needed oxygen treatment more frequently in addition to having delayed clinical improvement within 2 weeks. Being in the high-risk OSA group resulted in 5.08 times risk for ICU need, 1.95 times risk for supplemental oxygen need, and 1.55 times risk for clinical worsening in multivariable analysis.[27] Studies including a non-COVID population also indicate a longer length of stay related to OSA diagnosis.[24]

Risk factors for mortality among COVID-19 patients are common risk factors for OSA, such as age, obesity, HT, cardiovascular diseases, and DM. Cade et al.[28] defined OSA as an independent risk factor for mortality (OR:

Table 3: Factors associated with length of stay*

	Univariate analysis			Multivariate analysis		
	β	95% CI	p	β	95% CI	p
Age	0.10	0.06–0.15	<0.001			
Male gender	–1.26	–3.02–0.49	0.15			
HT	0.75	–1.03–2.55	0.40			
DM	0.50	-1.73–2.74	0.65			
Lymphocyte count (K/μL)	–0.001	–0.002–0.000	0.01	–0.001	–0.002–0.000	0.02
D-dimer (mg/L)	–0.002	–0.007–0.003	0.39			
Ferritin (μg/L)	–0.001	–0.004–0.003	0.69			
CRP (mg/L)	0.01	–0.008–0.02	0.25			
STOP-Bang total score	0.53	0.06–1.01	0.02	0.43	–0.44–0.90	0.07

*Coefficients given are unstandardized coefficients. HT: Hypertension, DM: Diabetes mellitus, CRP: C-reactive protein

1.39) after adjustment for age, sex, and BMI. Cariou et al.[11] reported an increased risk for mortality related to diagnosed and treated OSA by 2.8-fold within hospitalized diabetes patients.

Our study presented higher inflammatory biomarkers such as CRP and ferritin in high-risk OSA patients compared with low-risk OSA patients. This finding may be in accordance with increased underlying inflammation in patients with obesity and/or OSA.[22] Studies evaluating CRP measurements stated independent relationship between the presence of OSA, OSA severity, BMI, and CRP levels.[29] Increased IL-6 levels are also related to the presence of OSA, lower mean oxygen saturation, higher Epworth sleepiness scale, and higher BMI.[29]

Strengths and limitations

This cross-sectional multicenter study has limitations due to the study design. Patients were included in this study from outpatient clinics after they were discharged. Therefore, mortality, oxygen treatment, and length of hospital stay could not be evaluated. To avoid an imbalance, patients with ICU admission were excluded from the study because not every center included had an ICU. However, treatment modalities and initial disease severity were similar between centers because every center followed national treatment guidelines.

Conclusion

The prevalence of OSA within COVID-19 patients with favorable outcomes is similar to the general population. However, the length of stay is related to the presence of high-risk OSA. Our study, therefore, suggests that OSA is related to a delayed improvement of COVID-19 infection.

Conflicts of interest

There are no conflicts of interest.

Ethics Committee Approval

The study was approved by the Uludağ University Faculty of Medicine Clinical Research Ethics Committee (No: 2021-16/24, Date: 03/11/2021).

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Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept – A.U., N.A.A.Ö., M.K.; Design – A.E.C., A.A., B.Ö., F.C.; Supervision – E.D., A.G.D., F.C., D.E., E.U., A.U., M.K.; Funding – E.D., A.G.D., F.C., D.E., E.U., M.K., Ö.Ş.D., M.S., D.Y.; Materials – Ö.A.G., Z.Y., D.Z.; Data collection &/or processing – Ö.A.G., S.A., Ö.Ş.D., M.S., D.Y., E.T., A.E.C., D.B., A.A., Z.Y., M.B., B.Ö., D.Z., O.T.; Analysis and/or interpretation – N.A.A.Ö., Ö.A.G., O.T., A.U.; Literature search – S.A., E.T., D.B., M.B.; Writing – N.A.A.Ö., Ö.A.G., O.T., A.U., M.K., E.D., F.C., E.U., A.G.D.; Critical review – D.E., M.K., S.A., Ö.Ş.D., M.S., D.Y., E.T., A.E.C., D.B., A.A., Z.Y., M.B., B.Ö., D.Z.

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