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COMMENTARY

Obstructive sleep apnea and severe COVID-19 infection: is there a plausible link?

Commentary on Mashaqi S, Lee-Iannotti J, Rangan P, et al. Obstructive sleep apnea and COVID-19 clinical outcomes during hospitalization: a cohort study. *J Clin Sleep Med*. 2021;17(11):2197–2204. doi:10.5664/jcsm.9424

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Since March of 2020, the coronavirus disease 2019 (COVID-19) pandemic has seriously curtailed everyday life as it plunged humanity into a global health crisis. Despite the development of research occurring at lightning speed, much is still unknown about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Two landmark studies from Italy and the United States provided initial insight on comorbid conditions associated with increased risk of severe COVID-19 infection.[1,2] These comorbid conditions include older age, male, hypertension, elevated body mass index (BMI)/obesity, diabetes, and chronic obstructive lung disease. Interestingly, obstructive sleep apnea (OSA) was not evaluated as a potential independent risk factor for severe COVID-19 infection.

OSA shares the same comorbidities that have been determined to be significant contributors to poor outcomes related to COVID-19 infection.[3] Sleep deprivation, sleep disruption, repetitive nocturnal oxygen desaturations, and the resulting increase in systemic inflammation, reduced circulating nitric oxide levels, and dysregulated renin angiotensin system make an argument toward considering OSA as an independent risk factor for severe COVID-19 outcomes.[4–6] To date, multiple studies have evaluated the impact of OSA on COVID-19 outcomes, with implications pointing toward the disease as an independent risk factor for severe COVID-19 infection.

The Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) Study was one of the first studies analyzing the relationship between OSA and COVID-19 morbidity. The primary outcome was mechanical ventilation and/or death within 7 days of hospital admission. Multivariate adjustment showed that age, BMI, and OSA, among other factors, were independently associated with risk of death on day 7.[7] Maas et al,[8] utilizing a large socioeconomically diverse database comprising 10 hospital systems showed that patients with OSA had a higher risk of contracting COVID-19, and an increased risk of hospitalization and respiratory failure, even after adjusting for diabetes, hypertension, and BMI. Strausz et al,[9] utilizing a large registry of hospital discharge patients (FinnGen study), also showed increased risk of hospitalization in patients with OSA who contracted COVID-19, independent of age, sex, BMI, and comorbidities. A recent meta-analysis reviewed 21 studies (19 with a retrospective design) including 54,276 patients with COVID-19 and reported that OSA diagnosis was associated with poor composite outcomes, including severe COVID-19 infection, intensive care unit (ICU) admission, mechanical ventilatory support, and death (odds ratio: 1.72 [95% CI, 1.55–1.91]; $P < .00001$). BMI, however, was not adjusted for in this analysis. The majority of patients were considered overweight or obese.[10]

In this issue of the *Journal of Clinical Sleep Medicine*, Mashaqi et al[11] performed a retrospective review of 1,738 patients hospitalized with COVID-19. The authors examined the association between OSA and COVID-19–related clinical outcomes. Although the unadjusted model showed statistical significance for risk of ICU admission in patients with OSA hospitalized with COVID-19 infection, this effect dissipated once the model was adjusted for age, sex, BMI, and comorbid diseases. There are few large-scale studies evaluating OSA as an independent risk factor for severe COVID-19 infection in hospitalized patients. The unexpected finding of this study conflicts with results of prior studies and highlights the need for research on the plausible pathologic link between OSA and severe COVID-19 outcomes.

The results of Mashaqi et al are similar to the study by Cade and colleagues,[12] where an attenuation of the association of OSA to COVID-19 severe outcomes, including hospitalization, ICU admission, and mortality, was noted after adjusting for age, sex, BMI, and comorbid disease. A limitation of both studies was that OSA diagnostic criteria was based on the *International Classification of Diseases* (ICD) coding plus chart review (no formal confirmation with sleep testing). This may have underestimated the prevalence of OSA in the "non-OSA group." To this point, approximately 55% of the patients in Mashaqi et al study were considered to have a high clinical pretest probability of having OSA in the "non-OSA group" by using the Supersparse Linear Integer Model (SLIM) scoring system.[12] Second, one can argue that a higher COVID-19 severity index in the OSA group may have impacted the

treatment course of the patients by early initiation of respiratory therapy or early enrollment of patients into treatment trials, therefore indirectly impacting outcomes.

To date, no studies have specifically analyzed the severity of OSA (particularly nocturnal hypoxemia burden) and positive airway pressure (PAP) treatment adherence as modifiers for risk of severe COVID-19 infection. Cade and colleagues[12] completed an exploratory analysis showing a nonsignificant trend for an attenuated composite outcome for COVID-19 infection in PAP users. Preliminary data by Hwang et al[13] showed that continuous PAP (CPAP) adherence played a role in reduced infection rate among PAP adherent users when compared with nonadherent users. This was a retrospective analysis of patients with OSA with confirmed COVID-19 infection. The investigators also showed a correlation between OSA severity and infection rate (mild OSA: odds ratio, 1.21 [1.01–1.44]; moderate–severe OSA; odds ratio, 1.27 [1.07–1.51]).

Obesity is a strong risk factor for OSA and severe COVID-19 infection and remains a challenging cofounding variable despite statistical adjustments. The retrospective design of studies to date evaluating the association between OSA and severe COVID-19 infections is weakened by selection bias, unconfirmed OSA diagnostic methods, lack of data on OSA severity, and difficult to control confounding variables. The available data by no means conclude that OSA is or is not an independent risk factor for severe COVID-19 infection. We agree with Mashaqi and colleagues that OSA screening should be considered in patients with COVID-19 infection due to similarities in pathophysiological systemic inflammatory pathways and shared comorbid conditions leading to increased risk of severe infection. In addition, management of COVID-19 acute respiratory failure has moved away from early intubation to use of noninvasive strategies with improved outcomes. There are emerging data on benefits of PAP in avoiding intubation and invasive mechanical ventilatory support in hospitalized patients with acute respiratory failure from COVID-19.[14] For patients on CPAP for sleep apnea who develop COVID-19 infection, adherence to PAP therapy may be an important factor in clinical outcomes; however, no studies have examined this hypothesis.

Until we have clarity on the potential link between OSA and COVID-19 clinical outcomes, it remains judicious to provide counseling and close monitoring of patients with OSA infected with COVID-19 and encourage adherence to PAP therapy. Providers should be aware of and implement safe measures to allow continuation of PAP therapy while minimizing aerosolization risks of viral particles. Identifying underlying comorbid conditions such as OSA that may contribute to worsening of the COVID-19 infectious course is a crucial step in improving clinical outcomes.

CITATION

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DISCLOSURE STATEMENT

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