



Obstructive Sleep Apnea, COVID-19 and Risk for Long COVID: A Conundrum

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Abstract

The COVID-19 pandemic has made a major impact on global health and economy over the last year. With new variants emerging, several countries are currently going through a 3rd surge with a high risk for severe disease and mortality in the unvaccinated individuals. Despite significant data published over the last year, several questions remain unanswered and COVID-19 remains an enigma. Most importantly, risk factors that increase a person's risk for severe disease and mortality have not been clearly defined. Some of the standard comorbidities such as old age, obesity, diabetes, hypertension, respiratory or cardiovascular disease, and immunocompromised status have been reported as the major risk factors. Several pulmonology experts have hypothesized that OSA may be an independent risk factor for severe COVID-19, although the answer remains unclear. This article is a brief overview of currently available literature that links COVID-19 and OSA, focusing on OSA as an independent risk factor for severe COVID-19. It also emphasizes that early diagnosis and treatment of OSA with PAP is critical, as it decreases the risk for long-term (cardiovascular and cerebrovascular) complications thereby improving overall morbidity and mortality in these patients.

Keywords: Sleep Apnea; COVID 19; Long COVID; Public Health

Introduction

The current COVID-19 pandemic, caused by SARS CoV-2, (Severe acute respiratory syndrome) has made a major impact on global health and economy over the last year. With new variants emerging, several countries are currently going through a 3rd surge with a high risk for severe disease and mortality in the unvaccinated individuals. Research has evolved rapidly that resulted in emergency approval of several vaccines that protect against COVID-19.

Current knowledge on mode of invasion, pathophysiology, novel mutant variants, and management options continue to

evolve. Despite significant data published over the last year, several questions remain unanswered and COVID-19 remains an enigma. Most importantly, risk factors that increase a person's risk for severe disease and mortality have not been clearly defined. Some of the standard comorbidities such as old age, obesity, diabetes, hypertension, respiratory or cardiovascular disease, and immunocompromised status have been reported as the major risk factors.

Other comorbidities such as cerebrovascular stroke, hemodialysis, HIV, bronchiectasis, chronic obstructive pulmonary disease, and obstructive sleep apnea have also been evaluated as

risk factors for severe COVID-19, with indeterminate results. The 2 landmark studies that evaluated the risk factors were those from Italy and New York that provided the first insight on comorbidities that increased the risk for severe COVID 19 and/or death. Neither of these 2 studies mentioned chronic lung disease or obstructive sleep apnea (OSA) as risk factors [1,2].

Hypothesis on a link between OSA and COVID-19

Several pulmonology experts hypothesized that OSA may be an independent risk factor for severe COVID-19. Several pulmonology experts hypothesized that OSA may be an independent risk factor for severe COVID-19. This was because there were several similarities in risk factors between patients with OSA and the reported risk factors for severe COVID-19, such as old age, obesity, hypertension, and diabetes. For the same reasons, it was difficult to delineate if severe COVID-19 infections were due to these similar risk factors or if they were due to OSA by itself [3,4].

Obstructive sleep apnea

There are several types of sleep apnea but the most serious and frequently diagnosed type is the obstructive sleep apnea that affects about 1 billion people globally. It is a sleep disorder that causes breathing to spontaneously stop (apnea) and start several times during sleep. It results when muscles of the pharynx including the soft palate, uvula, tonsils, and tongue to relax and block the airway during sleep. Such episodes of apnea can happen 5-30 times during every hour or all night, during sleep. This causes periods of low oxygen supply and an increase in carbon dioxide levels in blood, thereby the brain and other organs during sleep, which may affect these organs in the long run that have an impact on morbidity and mortality [3]. The symptoms of sleep apnea include day-time sleepiness, loud snoring, sudden awakenings during sleep with gasping or choking episodes, morning headaches, poor concentration during the day, depression, irritability, and hypertension. Known risk factors for OSA include male gender, post-menopausal female, obesity, thick neck, opioid use, smoking, alcohol use, family history of snoring or OSA, hypothyroidism, facial abnormality and enlarged tonsils. On the other hand, OSA is a risk factor for developing long-term complications of OSA include hypertension, cardiac arrhythmias, myocardial infarction, and cerebrovascular stroke. It is unclear if OSA is an independent risk factor for severe COVID-19 [4].

In this review, we present currently available data on the link between COVID-19 and OSA, the benefit of PAP in preventing severe COVID-19, and cardiovascular complications from COVID-19 including those with long COVID syndrome.

Published studies that favor the hypothesis that OSA is an independent risk factor for severe COVID-19:

OSA an independent risk factor for severe COVID-19

One of the first review article was from Tufik, *et al.* described OSA to be an independent risk factor for severe COVID 19, mechanical ventilation and death. The authors postulated this based on their observance of similar risk factors for both OSA and COVID 19. They state that OSA results in hypoxic episodes with myocardial ischemia, resulting in hypertension, atrial and ventricular arrhythmias. It also causes hypoventilation, endothelial dysfunction in the pulmonary vasculature that may impede air exchange, and increases the invasion of SARS-CoV-2 in the lungs. This was one of the first reviews that highlighted a potential link between OSA and COVID-19. Several concerns were raised by the authors, including a possibility that OSA could independently facilitate SARS-CoV-2 infection and invasion, in addition to triggering cardiovascular complications [3,4].

Role of pro-inflammatory cytokines in OSA and COVID-19

Jose, *et al.* compared the pathophysiology of COVID-19 related acute respiratory distress syndrome (ARDS) and found similarities to that of severe community-acquired pneumonia caused by other viruses or bacteria. SARS-CoV-2 invades pulmonary parenchyma via the ACE-2 receptors located on type II pneumocytes in the lungs. This results in a sudden rapid increase in pro-inflammatory cytokines (tumor necrosis factor, interleukin-6, interleukin-beta1) culminating in a cytokine storm, leading to vascular thromboembolic phenomenon, multiorgan failure, and death. Hence, therapeutic interventions such as immunomodulators, that target this cytokine response are currently being used. Nevertheless, it is crucial to recognize that such cytokine inhibition must be balanced with maintaining an adequate inflammatory immune response to curtail the virus. One of the most serious complications of COVID-19 is vascular thromboembolism due to complex alterations in the thrombin pathway. Under normal conditions, thrombin generation is controlled by antithrombin III, tissue factor pathway inhibitor, and the protein C system. However, during the cytokine storm,

these pathways are dysfunctional, with decreased production and increasing consumption of anticoagulants. This procoagulant-anticoagulant imbalance leads to thrombosis, disseminated intravascular coagulation, ARDS, multi-organ failure, elevated d-dimer levels, as seen in patients with severe COVID-19 pneumonia and death. An interesting fact is that OSA, via intermittent hypoxia also triggers an inflammatory cascade, albeit in a milder fashion, resulting in an increase in proinflammatory cytokines, endothelial dysfunction, and cardiovascular complications in the long run [5,6].

Risk of severe COVID-19 in patients on treatment for OSA

The Coronavirus Sars-Cov2 and Diabetes Outcomes study (CORONADO) was one of the first studies that linked OSA and the risk for severe COVID-19. It was a multicenter observational study from France that analyzed 1317 patients with comorbidities such as diabetes and OSA, who were hospitalized for COVID-19. The primary outcome measured was invasive ventilation or death within 7 days of admission. The only caveat was that patients with a known history of OSA who were already receiving treatment with positive airway pressure (PAP), were included in the study, but not patients with undiagnosed or untreated OSA. A multivariate analysis showed that patients on treatment for OSA prior to admission had a higher risk of death by day 7 suggesting that a diagnosis of OSA is an independent risk factor for a poor COVID-19 outcome [7]. As there was no group with OSA patients not on treatment, it was not an ideal study to confirm the link between OSA and poor COVID-19 outcome. Patients with OSA have sleep deprivation and day-time sleepiness, both of which have been shown to be associated with a low-level release of inflammatory cytokines, including interleukins and tumor necrosis factor α , and neutrophilia [8].

Risk of OSA in COVID-19 related hospitalization

A Finnish group with Strausz, *et al.* examined whether the risk for contracting COVID-19 is elevated among OSA patients. They performed retrospective case-control study utilizing the Finnish nationwide health registries and the FinnGen Study cohort (n=260,405). A total of 305 patients with PCR-confirmed COVID-19 infection, including 26 (8.5%) who had OSA were included in the study. Severe COVID-19 that required hospitalization was noted in 83 patients (27.2%), of which 16 (19.3%) had OSA. In this study, OSA stood out as an independent risk factor for severe COVID-19 requiring hospitalization, after correcting for age, sex, body mass

index (BMI), hypertension, diabetes, coronary heart disease (CHD), asthma, and chronic obstructive pulmonary disease. However, OSA by itself, was not associated with the risk of contracting COVID-19. Authors concluded that the risk for acquiring COVID-19 by a patient with OSA was the same as a patient without OSA. However, patients with OSA had a five-fold risk of getting hospitalized with COVID-19 than non-OSA patients. This finding emphasizes the need to assess and recognize patients with OSA infection earlier, as this cohort may be at a higher risk for severe COVID-19. Interestingly, more women were hospitalized in this study compared to men. Limitations of this study was that non-hospitalized patients were not included in the study and hence a comparator arm was not available for milder forms of COVID 19 and hence data could be skewed [9].

Risk of acquiring COVID-19 and related complications in patients with OSA

Another study by Mass, *et al.* reviewed electronic medical records for an integrated health system comprising 10 hospitals in the Chicago metropolitan area to identify cases of COVID-19. Univariate and logistic regression tests were utilized to adjust for potential confounding variables such as diabetes, hypertension, and BMI. There was a total of 9405 COVID-19 infections, among which 3185 (34%) were hospitalized of which 1779 (19%) met the definition of severe COVID-19. OSA was more prevalent among patients requiring hospitalization than those who did not (15.3% versus 3.4%), and among those who progressed to respiratory failure (19.4% versus 4.5%) with statistical significance. After adjustment for diabetes, hypertension, and BMI, OSA was associated with ~ 2- fold increased risk for hospitalization/respiratory failure and ~8-fold greater risk for COVID-19 infection compared to a similar population [11]. This study had an advantage of collecting data from a diverse racial and socioeconomic group, but the major limitation was that coded data is not precise and may be unreliable.

Pre-test probability of OSA and risk for COVID-19

Another prospective multicenter observational study by Pekers, *et al.* compared clinical outcomes of COVID-19 at 4 weeks and 4 months in patients with low versus high probability of having OSA, based on a questionnaire. A secondary analysis compared clinical outcomes in patients with high vs low probability of having OSA, within 4 months of the COVID-19 diagnosis. Authors reported a higher risk for severe COVID-19 and poor outcome in the group

with a high pre-test probability of OSA after adjusting for age, sex, and other comorbidities [12] Researcher and participant bias with questionnaires was a major limitation of this study.

A large meta-analysis

The largest meta-analysis examining the potential link between OSA and severe COVID-19 was conducted by Hariyanto, *et al.* An elaborate search of PubMed and Europe PMC database was conducted using specific keywords such as OSA and COVID-19. Authors analyzed a total of 21 studies, of which 19 were retrospective in nature. Data on 54,276 patients with PCR confirmed COVID-19 and 4,640 patients with OSA were analyzed. This large meta-analysis showed that OSA was associated with composite poor outcome and ~ 2-fold higher risk for severe COVID-19, ICU admissions, the need for mechanical ventilation, and mortality. Based on their findings, authors recommended caution and close monitoring of patients with OSA to minimize the risk of complications and severity [13]. Also, simple questionnaires were suggested as screening tools for earlier identification of patients at risk for severe adverse outcomes. The major limitation of this study was that the BMI data for obesity, a major confounder, was not adjusted in this model. meta-analysis with previous studies. Another study published by Strausz, *et al.* evaluated 445 individuals with COVID-19. Comorbidities associated with either COVID-19 or OSA were selected as covariates. Authors also performed a meta-analysis with previous studies and concluded that the risk for contracting COVID-19 was equivalent for patients with or without OSA. However, among COVID-19 positive patients, OSA was associated with a higher risk for hospitalization and was as an independent risk factor for severe COVID-19 [9].

Studies that have concluded that OSA is not an independent risk factor for severe COVID -19

Role of CPAP use in patients with OSA and COVID-19

Cade, *et al.* analyzed electronic health records from a New England healthcare system to investigate if OSA is an unrecognized risk factor for severe COVID-19 (hospitalization, mechanical ventilation, ICU admission and death). Pertinent information regarding demographics, clinical notes, International Classification of Disease (ICD) diagnoses codes and history of continuous positive airway pressure (CPAP) usage in the year before the first COVID-19 test, were available in the database. A total of 4,668 patients were

evaluated, of which 443 (9.5%) with OSA had an increased all-cause mortality rate of 11.7%, compared to sleep apnea controls who were not on CPAP therapy [14]. However, when fully adjusted for demographics, BMI, asthma, COPD, hypertension, and DM, OSA fell out as an independent risk factor for COVID-19 related mortality. Interestingly, in an extended analysis, participants with CPAP use in the prior year had better outcome compared to participants without CPAP use. This was a study that emphasizes use of CPAP in OSA to decrease morbidity and mortality from COVID-19. Interestingly, the study by Strausz, *et al.* described above, was also included in a meta-analysis of 15,835 patients with COVID-19 and 1294 patients with OSA. Authors showed that OSA was associated with a two-fold increased risk for severe COVID-19 ($p < 0.001$). But when adjusted for BMI, the association lost statistical significance ($p = 0.13$). This was the only study that demonstrated the association between OSA and poor COVID-19 outcomes, before and after adjusting for BMI [9].

Risk for severe COVID-19 in OSA among PAP users vs non users

Another interesting study that looked at risk for acquiring COVID-19 in patients with OSA (with and without PAP use), was a cross-sectional telephone interview conducted in Iran, by Najafi, *et al.* A lower prevalence of COVID-19 was observed in patients who were receiving PAP for OSA and a higher prevalence of COVID-19 in patients with severe OSA who were not receiving therapy with PAP. The concern with use of PAP during the COVID-19 pandemic has been that it is an aerosol generating procedure with a risk of transmitting the SARS CoV-2 virus to people in the vicinity of PAP devices. However, it has been suggested that PAP device use in OSA improves overall quality of life, sleep and may even prevent hospitalizations due to severe COVID-19, and therefore it should be adhered to with additional measures to mitigate aerosol spread [15,16].

Is there a link between OSA and severe COVID-19?

As detailed above, most of the studies to date that have attempted to find an association between COVID-19 and OSA have used imperfect and inaccurate methods such as electronic chart review, databases, ICD codes, questionnaires, meta-analysis of retrospective studies, cross sectional surveys, or descriptive studies. None of these studies provide a definitive association or a lack of association between OSA and severe COVID-19. Nevertheless, most of these studies do indicate that there is definitely a link between

OSA and severe COVID-19 in patients with overlapping risk factors for OSA and COVID-19, such as sex, BMI/obesity, and hypertension. Also, *in vivo* animal studies and human studies have shown a common pro-inflammatory cytokine pathway in both conditions [8,17-19]. Hence, a well-designed prospective cohort study comparing short-term and long-term risk for severe COVID-19 in patients on PAP treatment and comparing it with those not on PAP treatment would offer more definitive answers.

OSA and Long COVID:

Long COVID is a syndrome characterized by the persistence or development of symptoms attributed to Covid-19, more than twelve weeks after initial infection. Clinical presentation varies but frequently reported symptoms include extreme fatigue that interferes with daily life, shortness of breath, difficulty thinking or concentrating (commonly known as “brain fog”), and sleep problems. A large study supported by the Researching COVID to Enhance Recovery (RECOVER) Initiative and the National Center for Advancing Translational Sciences (NCATS) has found that people with obstructive sleep apnea may have a higher risk for long COVID. Researchers evaluated anonymous electronic health records of 2.1 million adults age 21 and older, collected from databases, and found that between March 2020 and February 2022, 9% of adults in the study (86,716 people) had preexisting obstructive sleep apnea; 21% of people with COVID-19 (142,185 people) in the study were diagnosed with long COVID. Researchers calculated the odds of experiencing symptoms of long COVID in people with and without OSA and reported that the risk for long COVID was significantly higher in adults with OSA. In the largest group of people studied, those from the National COVID Cohort Collaborative, the risk for long COVID was ~ 75% higher for people with OSA compared to those without OSA and the risk was 30% higher in women. People with obstructive sleep apnea are encouraged to take preventive measures against COVID-19 [19].

Mandel, *et al.* studied the impact of preexisting OSA on the risk for probable PASC (post-acute sequelae of SARS-CoV-2 infection) in adults and children using electronic health record data from multiple research networks. Three large research networks within the REsearching COVID to Enhance Recovery initiative (PCORnet Adult, PCORnet Pediatric, and the National COVID Cohort Collaborative [N3C]) analyzed the risk of probable PASC in COVID-19-positive patients with and without OSA prior to pandemic

onset. It was reported that the unadjusted OR for probable PASC associated with a preexisting OSA diagnosis in adults and children ranged from 1.41 to 3.93. Adults with preexisting OSA were found to have significantly elevated odds of probable PASC. Patients with OSA may be at elevated risk for PASC after SARS-CoV-2 infection and should be monitored for post-acute sequelae [19].

Future prospectives

Based on population studies, it has been shown that OSA is a highly underrecognized and under-diagnosed condition. People with signs and symptoms of OSA as stated above should be encouraged to get a screening polysomnography test. Early diagnosis of OSA and management with PAP, of this simple but serious condition has several implications. It prevents ongoing hypoxia to several organ systems, further respiratory compromise, and any alteration of the renin-angiotensin system. It results in a long-term reduction in serum pro-inflammatory cytokines, that are known to increase the risk for myocardial infarction, hypertension, cardiac arrhythmias, and cerebrovascular strokes [20-22].

Conclusion

According to the National Healthy Sleep Awareness Project, the prevalence of obstructive sleep apnea is ~ 25 million adults and continues to be a threat for public health and safety. Individuals with history of deep snoring, gasping for breath during sleep and increased day time sleepiness should seek prompt medical care for a screening polysomnography to diagnose OSA. If diagnosed with OSA, they would benefit from the use of PAP, which has been shown to reduce overall morbidity and mortality by decreasing risk for myocardial infarction, hypertension, cardiac arrhythmias, and cerebrovascular strokes. Measurement of serum pro-inflammatory cytokines before and after PAP use is expected to show a reduction in these markers. A home-based polysomnography screening might be beneficial and might encourage patients to get screened earlier than spending time in the hospital, especially during and after the COVID-19 pandemic. Given intermittent hypoxic episodes that could impede neuronal function and metabolism, it is crucial to analyze the long-term risk of dementia and possible COVID-19 related encephalopathy in patients with untreated OSA. Until definitive data becomes available, patients with OSA and COVID-19 need to be closely monitored, and considered to be at high risk for severe COVID-19, hospitalization, mechanical ventilation, and death. These patients also need to be closely followed given the

risk for long COVID and preventive measures undertaken. Given positive clinical outcomes noted in patients with OSA who are adherent to PAP devices, it should be strongly encouraged.

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