A Review

Relationship Between Covid-19 & Severe Obstructive Sleep Apnea: A Systematic Review

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BACKGROUND

Since late December 2019, COVID-19, the disease caused by the novel coronavirus, SARS-CoV-2, has spread rapidly around the world, causing unprecedented changes in provided health care services. Patients diagnosed with sleep-disordered breathing (SDB) are subject to a higher risk of worse outcomes from COVID-19, due to the high prevalence of coexistent comorbidities such as obesity, hypertension and diabetes, features which are typically seen in patients with OSA. Additionally, treatment with positive airway treatment devices (PAP) can be challenging because of PAP-induced droplets and aerosols. In this context, sleep medicine practices are entering a new era and need to adapt rapidly to these circumstances, to provide the best care for patients with SDB.

PubMed was systematically searched up to 020620. Studies were included if they had examined the relationship between COVID-19 and OSA. Studies were included that were in English and had the full text available. The findings from this study suggest that many of the risk factors and comorbidities associated with OSA, which include obesity, hypertension, and diabetes mellitus, are associated with poor COVID-19 outcomes. There are plausible mechanisms by which OSA may independently increase one's risk of morbidity and mortality associated with COVID-19 and data from the newly published CORONADO study suggests that OSA treated patients may be at increased risk of death from COVID-19. It is clear that the pandemic has had a major effect on the treatment, management, and diagnosis of OSA and moving forward it may be necessary to explore new diagnosis and treatment pathways for these individuals.

The latter part of 2019 saw the emergence of a new coronavirus, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in Wuhan, China. The virus has now reached global pandemic proportions. Some individuals are at greater risk for adverse outcomes associated with the disease. These include older adults and those with respiratory and cardiovascular risk factors like obesity and diabetes mellitus[1]. The sleep disorder, Obstructive sleep apnoea (OSA) is characterized by repetitive partial or complete blockage of the airway during sleep, leading to interruptions in breathing, blood oxygen desaturation and arousal from sleep. OSA is associated with increased prevalence of hypertension (39%), obesity (34%), depression (19%), gastroesophageal reflux disease (GERD) (18%), diabetes mellitus (15%), hyper -cholesterolemia (10%), asthma (4%) [2]. Many of these factors have also been identified as risk factors for poor COVID-19 outcomes[3]. It is unclear whether the virus might pose an increased risk for patients with OSA.

The aims of this study were to conduct a systematic review of the rapidly emerging COVID-19 literature to determine:-

1. The relationship between

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obstructive sleep apnea (OSA) and adverse COVID-19 outcomes.
2. Potential causal mechanisms
3. What effect COVID-19 has had on OSA diagnosis
4. What effect COVID-19 has had on the treatment and management of OSA during this period.

Methods

Search strategy and selection criteria for Systematic searches using the Preferred reporting items for systematic reviews guidelines (PRISMA) [4] to identify studies that reported the association between COVID-19 and OSA were performed. Electronic searches were performed (from 2019 to December 2021) in PubMed. Following "COVID-19 sleep disorder" terms were used. The articles identified by the searches were reviewed along with any relevant references cited within them.

Inclusion & Exclusion Criteria

Papers were included if they examined the relationship between COVID-19 outcomes and OSA, or were related to the effect of COVID-19 pandemic on the diagnosis and treatment of this condition.

Papers were excluded if the full paper was not available or if they were not published in English. Total 251 potential studies were identfied after removal of duplicates. Abstract scanning yielded 26 for full text evaluation, from which 17 were included for the review[6-22].

Results

Of the 18 studies identified eight were mainly related to risk of COVID-19 mortality and 10 to diagnosis, treatment, and management. OSA and COVID-19 morbidity and mortality. Eight papers, seven from the original search[5,6,15,16,18-20] and one from reference searching[22] were examined. Of these, six contained original data[15,16,18-20,22]. Pazarli et al.[5] noted that common risk factors for COVID-19 mortality were shared with OSA, and these included increased age, hypertension, cardiovascular disease, lung disease, and diabetes mellitus. Likewise, McSharry[6] also noted that morbidity and mortality worldwide were particularly high amongst those with these comorbidities but that obesity, which is also commonly associated with OSA, might also be important.

Of the six studies with original data, Arentz et al. demonstrated that OSA was present in 28% of the 21 patients with coronavirus disease who presented to their intensive care unit[22]. Likewise, Bhatraju et al. found that 21% of patients with severe COVID pneumonia had OSA[15]. Gupta noted that of the first twenty-one patients admitted to a hospital in India with COVID-19 one had OSA[18]. Memsoudis et al. noted that of sixty ICU patients, 8.3% had OSA and of the non-ICU patients 6.3% had OSA[19]. He reflected that as EDS, excessive daytime sleepiness, EERS, enhanced expiratory rebreathing space, GERD, gastroesophageal reflux disease, IPF, idiopathic pulmonary fibrosis NIV noninvasive ventilation NIPPV noninvasive positive pressure ventilation OSA obstructive sleep apnoea PPE personal protection equipment PRISMA preferred reporting items for systematic reviews RAAS renin-angiotensin-aldosterone system ROS reactive oxgen species SARS-CoV-2 severe acute respiratory syndrome coronavirus 2 SDB sleep disordered breathing SFORL French Society of Otorhinolaryngology nearly all patients were obese the number of expected OSA patients was low and might reflect under-diagnosis of this disease. The Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) study aims to identify the clinical and biological features associated with the risk of poor COVID-19 outcomes in this study of people with diabetes hospitalized for COVID-19 Cariou et al. reported that treated obstructive sleep apnoea was independently associated with an increased risk of death on day 7 [16]. In a single case study, a 74-year-old male, with notable OSA, presented to the hospital with hypoxia and dyspnea. He tested positive for COVID-19 but was successfully extubated and treated with average volume-assured pressure support (AVAPS)[20].

What are the potential mechanistic pathways by which COVID-19 may affect OSA patients ?

A number of different biochemical and inflammatory mechanisms are associated with the pathophysiology and progression of OSA and its associated poor health outcomes, some of which have also been associated with COVID-19 disease. The sleep-time disruptions in breathing that accompany OSA are associated with intermittent blood gas disturbances (hypercapnia and hypoxemia) and surges of sympathetic activation. Increased inflammatory markers have been reported in OSA, but it remains to be determined if this is a result of the associated comorbidities[23]. Increased underlying inflammation however, may be of particular importance in obese patients as potentially it may contribute to the worsening hypoxemia and the cytokine storm that occurs in COVID-19 pneumonia patients and in those with subsequent multi-organ failure[24]. Results from a French study of 124 COVID patients indicated that obesity (BMI >30 kg/m 2) was a risk factor for invasive mechanical ventilation independent of age,

diabetes mellitus, and hypertension but frequency of OSA was not reported[25].

Recent studies have suggested that the sleep hormone melatonin may be beneficial for the treatment of COVID-19[26-28]. Melatonin may decrease oxidative stress, inflammation and the immune response, which may be particularly important in patients with OSA in whom these pathways are already activated. Activation of these pathways leads to a cytokine storm and subsequent progression to acute lung injury/acute respiratory distress syndrome (ARDS) and often death. Melatonin may also improve sleeping quality, which might also be beneficial for better clinical outcomes for COVID-19 patients [26].

There is increasing evidence to suggest that vitamin D deficiency may be a risk factor for CVD . Vitamin D may play an important role in the suppression of harmful reactive oxygen species (ROS) and, inflammatory markers and may stimulate protective endothelial nitric oxide production[29]. In a study of 176 children, Kheinrandish-Gozal et al. demonstrated that OSA was independently associated with higher hsCRP and lipids, and lower vitamin D[30]. Furthermore, multiple logistic regression identified a strong effect of African American race on lower vitamin D levels, and showed the severity of OSA as measured by the apnoea hypopnea index (AHI) correlated with lower vitamin D[30]. Vitamin D levels may be influenced by both diet and ethnicity. Vitamin D also enhances cellular immunity, in part by reducing the cytokine storm induced by the innate immune system, and it has been suggested that low levels of vitamin D may in part be associated with poor COVID-19 outcomes[31]. A recent study from the UK Biobank, however, did not find any evidence to support this[32] . They examined the data from 348,598 UK Biobank participants of whom 449 had confirmed COVID-19 infection. They found that While vitamin D was associated with COVID-19 infection, this did not persist after adjustment for confounders. They concluded that 'their findings did not support a potential link between vitamin Fig. 1. PRISMA flow chart. Concentrations and risk of COVID-19 infection, nor that vitamin D concentration may explain ethnic differences in COVID-19 infection'[32].

OSA is observed in a large proportion of individuals with resistant hypertension. A recent meta-analysis demonstrated that OSA is associated with higher Angiotensin II and aldosterone levels, especially in hypertensive patients. It has been suggested, therefore, that OSA may lead to an increase in blood pressure through stimulation of the renin-angiotensin-aldosterone system (RAAS) [33]. The Angiotensin converting enzyme 2 (ACE2) has been identified as the entry receptor of SARS-CoV-2[34] but unlike ACE, ACE2 does not convert Angiotensin I to Angiotensin II. Further investigation is therefore warranted to determine whether individuals, in whom there is an increased stimulation of the RAAS in OSA, are at increased risk of the cardiovascular complications and comorbidities seen in COVID-19 patients.

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease that is associated with oxygen desaturation and pulmonary arterial hypertension. OSA is often reported in patients with IPF and recent PF guidelines have recognized OSA as an important associated comorbidity that can affect patient's survival[35]. It is recommended that newly diagnosed IPF patients should be referred to sleep centers for the diagnosis and treatment of OSA[36]. Fibrotic changes have also been seen in patients after COVID-19[37]. It is therefore important that patients who have had COVID-19 and who have fibrotic changes are screened for potential OSA. It is as yet unclear whether OSA patients with existing fibrotic changes may be at increased risk from the effects of COVID-19.

The effect of COVID-19 pandemic on the treatment and management of OSA. According to the available evidence, SARS-CoV-2 transmission occurs through droplets. Exhaled aerosol size depends on a number of factors including the characteristics of the fluid, the force and pressure at the moment of emission, and the environmental conditions[38]. Treatment of OSA with continuous positive airway pressure (CPAP) improves the health and well being of patients and improves hypertension management and control in those with moderate-to-severe disease. CPAP is included in the noninvasive ventilation (NIV) category and is included in the WHO list of high-risk aerosol-generating procedures[38]. The use of CPAP may therefore put those in its vicinity at increased risk of viral exposure and at a high risk of contagion [7]. It is for this reason that Barker et al. have argued that community CPAP and NIV should be stopped unless it is medically necessary for life support[8]. They acknowledge that evidence is limited but suggest that continued CPAP use might put other members of the household/carers at increased risk. In response to this, Baker and Sovani have argued that there are risks from stopping NIV and CPAP for patients[9]. Cessation of CPAP treatment may be associated with a return of symptoms. These may include effects on daytime sleepiness, concentration, memory, and mood. A return of symptoms, in particular, excessive sleepiness, may also be harmful to the general public as a result of poor concentration and increased risk of performance errors and road traffic accidents[39], OSA is a relatively common disorder with many of the 1.5 million individuals diagnosed in the UK alone being treated with CPAP. Given that the pandemic is affecting millions of people globally, it is likely that

many OSA CPAPetreated patients will be affected. Ways to reduce viral shedding from positive airway devices are therefore important. Bacterial/viral filters are being designed to trap particles and recently Kryger et al. described how the use of Enhanced Expiratory Rebreathing Space (EERS) might help reduce viral shedding[10]. They suggest, however, that an individual with severe OSA who contracts COVID-19 might be best managed in a healthcare facility where staff might be able to take necessary precautions and use Personal Protection Equipment (PPE). In the UK, the British Sleep Society with the OSA Alliance (incorporating British Thoracic Society, British Sleep Society, Association for Respiratory Technology and Physiology, Sleep Apnoea Trust Association) has just released guidelines with regards to the use of CPAP during the pandemic[40]. The guidance suggests that people with OSA should continue to use their CPAP at home as normal but suggests that individuals might wish to consider taking steps to distance themselves from vulnerable household members by changing bedrooms or stopping CPAP for a short time. It encourages patients to persist with CPAP when experiencing symptoms of respiratory infection. The current National Health Service guidance states for patients who remain at home during the coronavirus pandemic, to continue with their usual method of ventilation. M.A. Miller, F.P. Cappuccio / Sleep Medicine Reviews 55 (2021) 101382 7.

In France, the French Association of Otorhinolaryngology and Sleep disorders (AFSORL) and the French Society of Otorhinolaryngology (SFORL) put forward a summary of the measures for continuing the treatment of sleep apnoea syndrome in these new practice conditions. Interestingly, in a separate study of 7485 patients, it was noted that compliance to CPAP improved during lockdown compared with data one month before and when compared with the same period the preceding year. It was suggested that this may be the result of publicity regarding COVID-9, which has been described as a disease that affects the airways and a fear of hospitalization may have motivated patients to adhere to treatment. Spending more time at home might have also led to an increased opportunities to sleep and to use the CPAP treatment[21].

Oral devices may also be used for the treatment of OSA. Given that many dental procedures generate aerosols, there is a concern that viral droplets may remain suspended in the air. Thus, While oral appliance treatments may be low-risk procedures, there may be a risk to sleep patients from other procedures conducted at dental practice. Likewise, due to the transmission risk, the procedures for cleaning oral sleep appliances, which include a mandibular advancement, appliances for snoring, and sleep apnea, may need to be reviewed [12].

The effect of COVID-19 on OSA diagnosis

OSA is very prevalent worldwide, and given that the comorbidities of OSA patients are shared with those of COVID-19 patients who experience adverse outcomes, it may be of great importance to ensure that OSA patients receive effective CPAP therapy if confronted with COVID-19 infection. A recent study by Grote et al. assessed the impact of the COVID-19 pandemic on the management of sleep disordered breathing (SDB) in patients in nineteen European countries. In 31 of the total 40 participating centers, patients were unable to physically attend because of travel restrictions. It was found that major changes to the services provided occurred during the pandemic. For the diagnosis of OSA, it was reported that, prior to COVID-19 pandemic, 92.5% were used lab Polysomnography, 87.5% used Polygraphy at home and 30% used Telemedicine. During the pandemic, in-lab polysomnography had significantly reduced to 20%, at-home Polygraphy to 32.5%, and Telemedicine based diagnosis was used in 27.5%. They also reported that commencement of treatment for SDB by various types of positive airway pressure therapy were equally reduced in the vast majority of centres and countries. Furthermore, staffing level in the sleep medicine service were reduced to 25% for physicians and to 19% for nurses/technicians compared to pre-pandemic levels[13].

In China, in high epidemic areas, such as Wuhan and nearby cities in Hubei province, sleep study and noninvasive positive pressure ventilation (NIPPV) were suspended except in case of emergency whereas for areas with low COVID-19 it was decided that in-lab sleep studies could be performed in 'at risk' individuals providing the possibility of COVID-19 infection could be excluded and with the proviso that appropriate PPE is available and virus control procedure are followed. Other sleep services and follow-up appointments are provided via online services[11]. In the US, the American Academy of Sleep Medicine (AASM) issued revised recommendations on 27th April 2020 that include the postponement of in-laboratory sleep studies for all patients[41]. For necessary testing, it recommends that consideration is given to using single-use, fully disposable devices and/or components. If reusable devices are used, these must be cleaned and sanitized according to CDC disinfection standards and manufacturer's instructions and that personnel should have appropriate PPE. It advises that a reusable device should be removed from service for at least 72 h in addition to disinfection before its next use[41]. Similar procedures should be followed for home testing and the use of a mail

delivery service would ensure that patients do not have to leave their home to receive or return the device[14,41]. Telemedicine may play a more important role in the diagnosis and management of these conditions. For individuals who do need to be seen in sleep clinics, it is clear that measures to screen individuals arriving at the clinics as well as increased personal protection measures and sanitization measures need to be implemented. New procedures for the treatment of patients requiring ventilation who become infected with COVID-19 may be required to prevent spread to staff, carers or family members[14].

DISCUSSION

This comprehensive systematic literature review is consistent with a recent study of 1099 COVID-19 patients, which did not specifically look at OSA, but which showed higher rates of chronic obstructive pulmonary disease (COPD), diabetes and hypertension in patients who were admitted to intensive care units, required mechanical ventilation or died[42]. In the majority of the reviewed studies, it has not been possible to establish whether OSA is simply a comorbidity that is associated with Covid-19 morbidity and mortality or whether is it a potentially and independent risk factor for poor COVID-19 outcomes. However, the CORONADO study has examined this in more detail[16]. Data published online on May 29th, documents the clinic characteristics of 1317 individuals with diabetes in the study prior to admission to hospital with coronavirus symptoms; of these, 1189 individuals had treated OSA. The study demonstrated that dyspnea, lymphocyte count, Creactive Protein, and AST measured on admission were independent predictors of the primary outcome of tracheal intubation and/or death at day 7. Age, treated obstructive apnoea and microvascular and macro-vascular complications were also independently associated with risk of death at day 7[16]. Further studies are therefore warranted to establish this potentially causal relationship between OSA and COVID-19 outcomes, both in individuals with and in those without diabetes.

In a study by Voncken et al. on “Impact of obstructive sleep apnea on clinical outcomes in patients hospitalized with COVID-19” The prevalence of OSA did not differ between patients with or without COVID-19, but mortality and hospital length of stay were increased in patients with OSA and comorbid COVID-19. Hence, OSA should be included in COVID-19 risk factor analyses, clinicians should be aware of the association, and the mechanism should be further explored[44]. There are a number of plausible pathways by which COVID-19 might have an adverse effect on OSA patients and further research is warranted to investigate these pathways. Furthermore, given that recent studies suggest that melatonin may be beneficial for the treatment of COVID-19[26-28] it remains to be seen if sleep and treatment for sleep disorders may have beneficial effects on COVID-19 outcomes. Many COVID-19 patients suffer pulmonary fibrosis which itself is a risk factor for future development of OSA. Careful monitoring of discharged patients for thrombotic and fibrotic effects and subsequent OSA development are warranted. Moving forward, it is necessary that guidelines are reviewed so that as new knowledge is acquired, the best practices for the diagnosis and treatment of sleep disorders under these restrictive pandemic conditions may be developed. Many sleep laboratory teams have been assisting with the respiratory effects suffered by COVID-19 patients, and it is clear for 'normal' sleep services to resume all sleep center stuff including physicians, sleep technicians, and respiratory physiotherapists or respiratory nurses will need ongoing training in updated clinical knowledge of the COVID- 19 pandemic. It will be necessary to continuously review the practices and to develop new safe operating procedures with reference to guidelines from the government, scientific societies and national authorities. The emergence of disposable kits for overnight sleep studies is important as they may provide a new and safe way for the diagnosis of sleep conditions, under these restrictive conditions. Carlotta Mutti et al. explained as Obstructive sleep apnea (OSA), is a broadly diffused, curable chronic low-grade inflammatory disease sharing impressive clinical and pathogenetic features with Covid-19. Moreover, a potential role of OSA as a detrimental factor for Covid-19 severity has been hypothesized. Continuous positive airway pressure (CPAP) is the mainstay treatment for moderate-severe OSA, but the beneficial effects of ventilation strongly depend on medical expertise and on the patient's adherence and compliance. Although several papers have analyzed the overlaps and outcomes of OSA and Covid-19, limited attention has been dedicated to ventilatory adherence and management of OSA cohorts exposed to Covid-19[45]. In a study by Satu Strausz et al. he said that risk for contracting COVID-19 was the same for patients with OSA and those without OSA. In contrast, among COVID-19 positive patients, OSA was associated with a higher risk for hospitalization. Our findings are in line with earlier work and suggest OSA as an independent risk factor for severe COVID-19[46].

CONCLUSION

The findings from this study suggest that many of the risk factors for OSA are associated with poor

COVID-19 outcomes. There are plausible mechanisms by which OSA may be associated with poor outcomes and further studies are required to corroborate the data from the CORONADO study which suggests that treatment for OSA is independently associated with the risk of death from COVID-19. The pandemic has had a major effect on the treatment, management, and diagnosis of OSA and moving forward it may be necessary to explore new diagnosis and treatment pathways for these individuals. This may include increased telemedicine and the use of disposable diagnostic tools and noncontact sleep surveillance for sleep apnoea diagnosis. Those already diagnosed but waiting treatment may need priority at this time to mitigate any potential increase in risk.

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