Review Article | Palliative Medicine and Palliative Care for Serious or Advanced Diseases

Respiratory disorders and their association with clinical outcomes in COVID-19: a narrative review of current literature※

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Background and Objective: The coronavirus disease 2019, also known as COVID-19, has caused significant worldwide morbidity and mortality. Given the direct effect of severe acute respiratory syndrome virus-2 (SARS-CoV-2) on the respiratory system, it is important that clinicians who manage chronic respiratory conditions are familiar with the pathophysiology and impact of COVID-19 on pre-existing respiratory disease.

Methods: Literature review relating to COVID-19 and respiratory disorders from PubMed and Google Scholar was conducted, with aim to encompass all publications relating to the most commonly encountered respiratory diseases in clinical practice, namely chronic obstructive lung disease (COPD), asthma, interstitial lung disease (ILD), obstructive sleep apnea (OSA), as well as obesity given it's known effect on both gas exchange and mechanistic aspects of respiration. The publications were analyzed for relevance to clinical implications and pathophysiologic mechanisms. Additional manual literature review was conducted based on citations from large review articles and society guidelines/statement papers.

Key Content and Findings: Certain respiratory disorders such as COPD, ILD, OSA, and obesity carry higher burden of morbidity and mortality associated with COVID-19. Surprisingly, and in contrast to previously studied viral epidemics, asthma does not carry increased associated risk of contracting the virus or worse clinical outcomes.

Conclusions: A thorough understanding of the mechanisms responsible for control of breathing and the effect of COVID-19 on pulmonary pathophysiology will allow clinicians who manage chronic respiratory disease to effectively predict associated clinical outcomes as well as improve management strategies.

Keywords: Coronavirus disease 2019 (COVID-19); clinical outcomes; pathophysiology; respiratory disorders; review

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Introduction

The coronavirus disease 2019, also known as COVID-19, pandemic has caused by the emergence of a new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to significant morbidity and mortality worldwide (1).

The spectrum of COVID-19 disease manifestation ranges from asymptomatic illness to severe pneumonia, respiratory failure, and death (2). Individuals with certain co-morbidities have been identified to be at greater risk for adverse outcomes related to COVID-19, including older age, male sex, respiratory and cardiovascular disease, obesity, smoking and diabetes mellitus, among others (3-5). A prior multi-hospital cohort study examining clinical outcomes of COVID-19 revealed pre-existing respiratory disease to be an important predictor of mortality and disease severity (6).

Given direct impact of COVID-19 on the respiratory system, it is expected that clinicians who manage patients with chronic respiratory conditions be familiar with any disease-specific risk factors as well as associated clinical outcomes. Understanding the pathophysiology of the effects of COVID-19 on the pulmonary system will not only aide in disease management but also in predicting outcomes and patient counseling.

This narrative review aims to examine the effect of COVID-19 on pulmonary pathophysiology as well as clinical sequalae and disease burden in patients with pre-existing respiratory disorders, specifically chronic obstructive lung disease (COPD), asthma, obstructive sleep apnea (OSA), interstitial lung disease (ILD), and obesity. We present this article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1427/rc).

Methods

We performed a literature search for publications regarding clinical outcomes of COVID-19 and respiratory diseases up until 11/30/2022. Databases used for the search included PubMed and Google Scholar. The aim of our literature search was to encompass all publications regarding the clinical outcomes of COVID-19 as it relates to the most commonly encountered respiratory diseases in clinical practice, namely COPD, asthma, interstitial lung disease (ILD) and obstructive sleep apnea (OSA). Obesity was also included as a respiratory disorder in this review given its known effect on both gas exchange (7) as well as mechanical aspects of respiration (8). Additional articles were included following a manual review of publications cited in large review articles. There was no set timeframe for literature search given novelty of COVID-19. Pertinent data was obtained from articles reviewed and description of those findings are included in the sections that follow. The review process for this article is summarized in *Table 1*.

COVID-19 and impact on pulmonary pathophysiology

COVID-19 has been shown to affect multiple facets of the respiratory system including the conducting airways, respiratory epithelium and alveoli as well as pulmonary vascular endothelium (9-12); all of which contribute to the resultant hypoxemia (13).

One of the well described effects of COVID-19 on pulmonary pathophysiology is the phenomenon known as "silent hypoxemia", which is characterized by pronounced arterial hypoxemia without corresponding sensation of dyspnea (14-16). It is important for clinicians to correctly recognize hypoxemia in patients with COVID-19 given that the severity of hypoxemia is an independent risk factor for in-hospital mortality as well as increased risk of intensive care unit (ICU) admission (17,18).

Dyspnea is the sensation of "unpleasant breathing", subjective to the patient, and generally occurs when the patient is unable to respond to demands in ventilation (19,20). Hypoxemia leads to dyspnea by stimulation of the carotid bodies, which in turn signal to the medulla oblongata and pons in the brainstem, responsible for control of respiratory drive (21,22). Increased output from this respiratory control center results in increased phrenic nerve output to the diaphragm, causing increased minute ventilation (V_E) (21,23) as well as increased output to the cerebral cortex, known as corollary discharge, which is responsible for the sensation of dyspnea (24), see *Figure 1*.

The degree of hypoxia required to produce an increase in V_E is considerable, with minimal change in V_E associated with PaO_2 ranging from 90 to 60 mmHg, however an exponential rise in V_E is observed when PaO_2 drops below 60 mmHg (25). Similarly, a comparable degree of hypoxemia (PaO_2 below 60 mmHg) is required to induce the sensation of dyspnea, when $PaCO_2$ levels are normal (less than 40 mmHg) (26). In contrast, the hypercapnic response is linear and hence has a more pronounced impact on V_E and the sensation of dyspnea. In fact, the respiratory control centers in the brainstem are highly sensitive to small changes in $PaCO_2$, with an increase in $PaCO_2$ of

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Table 1 The search strategy summary

Items	Specification
Dates of search	10/15/2022–11/30/2022
Databases	PubMed and Google Scholar
Search terms used	Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and 2020 science committee report on COVID-19, Global Initiative for Asthma (GINA) guidance on COVID-19 and asthma 2021, clinical outcomes in COVID-19, COVID-19 and lung pathophysiology, COPD and COVID-19, Asthma and COVID-19, Interstitial lung disease and COVID-19, obstructive sleep apnea (OSA) and COVID-19, obesity and COVID-19, obesity and ventilation, control of breathing
Timeframe	No limitations given novelty of disease
Inclusion and exclusion criteria	Inclusion criteria: review articles, meta-analyses, systematic reviews, case series, prospective studies, society guidelines, editorials in peer-reviewed journals; exclusion criteria: articles from news media, online blogs
Selection process	Articles selected by D.G. Venkat and approved by M.S. Badr

COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019.

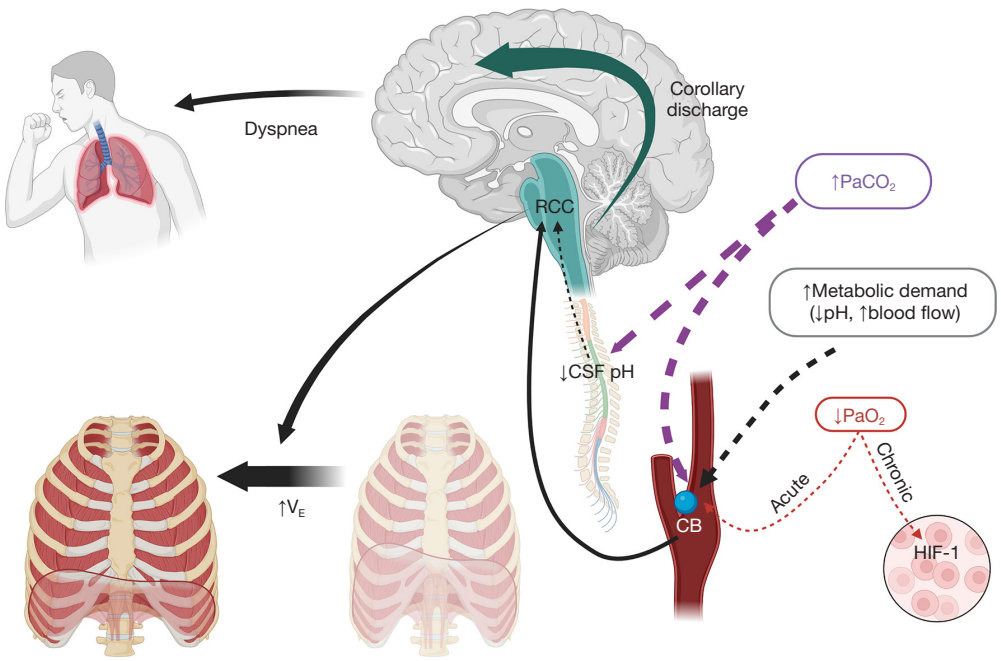

Figure 1 Factors influencing control of breathing and dyspnea, with disproportionate effect of $PaCO_2$ *vs.* PaO_2. Created with BioRender.com. RCC, respiratory control center; CB, carotid body; HIF-1, hypoxia inducible factor-1; CSF, cerebrospinal fluid.

just 10 mmHg resulting in significant increases in V_E and corresponding sensation of dyspnea (27). In addition, an increase in background PCO_2 to more than 39 mmHg is required to elicit an effective increase V_E, even in cases of severe hypoxemia (28).

There SARS-CoV-2 may exert direct effects on various aspects of the mechanistic pathway involved in control of breathing. For instance, it is known that there is expression of angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV-2, in the carotid bodies (29). As mentioned previously, these chemoreceptors in the carotid bodies are normally stimulated in response to hypoxemia (21), however this effect may be blunted by SARS-CoV-2.

Another contributing factor to silent hypoxemia,

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though not specific to COVID-19, is shifting of the oxygen dissociation curve to the right due to fever (30). For instance, when pH and $PaCO_2$ are normal, a temperature of 40 ℃ will induce a decrease in oxygen saturation (SaO_2) of approximately 10% for the same PaO_2 (31). Despite the decrease in oxygen saturation, respiratory drive remains unaltered as changes in SaO_2 have no effect on stimulation of carotid bodies, which respond only to changes in PaO_2 (21,32).

COPD

Given the paucity of available population studies, it is currently unknown whether having COPD alters the risk of contracting SARS-CoV-2. One population survey with random sampling from Germany (33), along with studies in the community of people tested for SARS-CoV-2 have not shown chronic respiratory disease to be an independent risk factor for contracting the virus (34,35).

In regard to risk of hospitalization and severe disease with COVID-19, there appears to be a higher risk associated with COPD. The reported prevalence of COPD among hospitalized patients with COPD has been shown to be higher than overall disease prevalence in multiple studies (4,36-38). COPD has also been shown to be an independent risk factor for hospitalization [hazard ratio =1.55 (95% CI: 1.46–1.64)] in a UK-based primary care cohort study of over 8 million patients (39).

Although clinical implications remain unclear, basic science offers insight into the apparent finding that COPD may be a risk factor for increased disease severity in COVID-19 (40).

It has been shown that the SARS-CoV-2 viral spike protein binds to angiotensin-converting enzyme 2 (ACE2) receptor during viral attachment to host cells and that viral entry is also facilitated by transmembrane serine protease 2 (TMPRSS2) (41-44). Therefore, susceptibility and clinical outcomes of SARS-CoV-2 infection may be affected by varying expression of ACE2 and TMPRSS2 (45). ACE2 mRNA expression has been shown to be increased in bronchial epithelial cells of COPD patients when compared to control subjects (46). ACE-2 expression was also noted to be increased in current smokers when compared to former and never smokers (47-49). In addition, there is evidence of increased ACE-2 expression associated specifically with nicotine exposure (50,51). Similarly, decreased expression of ACE-2 would suggest decreased viral entry. Although yet to be studied in the COPD population, inhaled corticosteroid use (52) has been shown to decrease ACE-2 expression in airway epithelial cells of asthmatic patients when compared to those who were not taking ICS (53). Again, important to note, is that clinical implications remain unclear and ACE-2 expression alone has not been shown to translate into increased susceptibility or increased disease severity.

As per the most recent expert consensus, the 2020 Global Initiative for Chronic Obstructive Lung Disease (GOLD) science committee report on COVID-19 and COPD summarizes that there does not appear to be an increased risk of acquiring COVID-19 in patients with COPD, however they do appear to be at increased risk of developing severe disease and death (54).

Asthma

Prior epidemiologic data regarding influenza H1N1 virus and its close association with asthma (55,56) would lead one to be concerned regarding the possibility of a similar association with COVID-19. Multiple studies have aimed at addressing the association between asthma and COVID-19 in regard to both risk of acquiring COVID-19 as well as any associated increase in morbidity.

Regarding asthma increasing risk of infection with SARS-CoV-2, there have been numerous studies, however data has been largely conflicting. Two recent real-life studies reported an increased frequency of COVID-19 in patients with asthma when compared to those without in both Spain (1.41% *vs.* 0.86%) (57) and Korea (2.9% *vs.* 1.6–2.2%) (58), suggesting that asthma increases susceptibility to contracting COVID-19. In contrast, a systematic review and meta-analysis evaluating risk of COVID-19 infection, hospitalization and morbidity in asthma patients revealed a decreased risk of acquiring COVID-19 (relative risk reduction of 17%) when compared to non-asthmatics (59).

The same studies mentioned previously also evaluated the association between asthma and COVID-19 disease severity and found no increase in risk when compared to non-asthmatic patients (57-59).

The conflicting evidence regarding asthma and association with clinical outcomes in COVID-19 leads to speculation regarding differences in asthma phenotypes, in particular Th2-high (allergic) and Th2-low (non-allergic) (60). Th2-low phenotype may be associated with an increased risk of severe COVID-19 as suggested by data from a Korean cohort study revealing greater risk of SARS-CoV-2 test positivity and severe clinical outcomes of COVID-19 in patients with non-allergic asthma when compared to those with allergic asthma (61).

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Patients with Th2-low asthma are immunologically primed for severe COVID-19 and cytokine storm due to chronic subclinical inflammation and metabolic dysregulation as a result of comorbidities such as diabetes and obesity as well as older age (62). Studies have also shown Th2-low asthma cytokines [interleukin (IL)-12, IL-17A, tumor necrosis factor (TNF)] upregulate ACE2 expression, whereas Th2-high/allergic asthma cytokines (IL-4 and IL-13) downregulate ACE2 expression in airway epithelial cells *in vitro* (63). Further supporting the protective effect of Th2-high asthma is evidence of downregulation of ACE2 gene expression (64) as well as upregulation of circulating soluble ACE2 which could competitively inhibit the ability of SARS-CoV-2 to bind to airway cell membranes (65).

As summarized in the 2021 Global Initiative for Asthma (GINA) strategy report, there does not appear to be any associated increased risk of both acquiring COVID-19 or having worse clinical outcomes from COVID-19 in patients with well-controlled, mild to moderate asthma (66). However, risk of COVID-19 related death increases in patients with poorly controlled asthma with recent oral corticosteroid use (67,68) as well as hospitalized patients with severe asthma (69). Similarly, Centers for Disease Control (CDC) guidelines concur that although evidence is conflicting regarding overall asthma mortality related to COVID-19, there does appear to be increased risk of hospitalization, ICU admission, and hospital readmission in patients with COVID-19 and underlying asthma (70).

Interstitial lung disease (ILD)

The impact of COVID-19 on ILD is of great concern given the degree of baseline impairment of lung function and increased risk of exacerbations due to viral illnesses (71). Several studies have sought to explore this association and its clinical implications further, with results suggesting that ILD patients have worse clinical outcomes in COVID-19 when compared to patients without ILD. In a study based at UK and European ILD centers, preexisting ILD was associated with significantly higher mortality due to COVID-19 [hazard ratio (HR) =1.6 (95% CI: 1.17–2.18)], when compared to age-, sex-, and comorbidity-matched controls without ILD (72). A case control study conducted in 6 medical centers in Boston, MA revealed a four-fold increase in adjusted risk of death in patients with pre-existing ILD (73). A multi-center, observational study based in France described a case fatality rate of 35% among patients with idiopathic fibrotic ILD and 19% in patients with non-fibrotic or other ILDs (74).

Consideration must also be given to the development of fibrotic lung disease after COVID-19 in patients without pre-existing ILD, given the emergence of post-COVID-19 syndrome, defined as the persistence of post-acute symptoms beyond 12 weeks (75). A systematic review of short- and long-term rates of post-acute sequelae of SARS-CoV-2 infection revealed pulmonary fibrosis was identified in 7% of patients after at least 6 months since COVID-19 diagnosis or hospital discharge (52). Similarly, other studies evaluating fibrotic changes seen on lung imaging in patients with ILD, show persistent fibrotic changes in 12% or less of patients at 5–7 months post COVID-19 (76,77). Another systematic review and meta-analysis evaluating lung imaging and pulmonary function testing within 12 months following hospitalization due to COVID-19 revealed opacities suggestive of lung fibrotic lesions in approximately 29% (78). A prospective, longitudinal, cohort study evaluating respiratory outcomes at 3-, 6-, and 12-months post hospitalization due to COVID-19 revealed temporal improvement in physiologic and radiologic parameters in most patients, however radiologic changes persisted in approximately 24% of patients (79). These findings are consistent with previous studies evaluating post-infectious sequelae from other coronaviruses (SARS-CoV-1, MERS-CoV) and influenza H1N1, which have described persistent interstitial and fibrotic lung abnormalities in approximately one third of patients (80,81).

Obstructive sleep apnea (OSA)

OSA and COVID-19 are both pro-inflammatory states (82), and it has been previously reported that not only is OSA a risk factor for pneumonia, but that the severity of OSA correlates to pneumonia severity (83). In addition, OSA has been shown to be associated with increased systemic inflammation due to sleep disruption and repetitive nocturnal oxygen desaturations as well as dysregulated renin angiotensin system in COVID-19 (84,85). This would lead one to consider OSA to be an independent risk factor for outcomes related to COVID-19. However, differentiating OSA as an independent risk factor from simply an associated comorbidity in COVID-19 becomes challenging, as both OSA and COVID-19 share the same comorbidities known to contribute to poor outcomes in both disease states (86). Several studies have sought to further clarify the implications of OSA on COVID-19 outcomes, however data remains limited and conflicting.

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The Coronavirus SARS-CoV2 and Diabetes Outcomes Study (CORONADO) identified OSA to be an independent risk factor for 7-day mortality [odds ratio (OR) =2.8 (95% CI: 1.46–5.38)] (87). A large retrospective study utilizing a socioeconomically diverse database spanning 10 hospital registries, showed that patients with OSA have an increased risk of contracting COVID-19 [OR =1.65 (95% CI: 1.36–2.02)] as well as respiratory failure [OR =1.98 (95% CI: 1.65–2.37)], after adjusting for age, BMI, and DM type 2 (88). A smaller retrospective study, after adjusting for sex, BMI and comorbid disease, found an increased risk of hospitalization in patients with OSA and COVID-19 [OR =2.93 (95% CI: 1.02–8.39)], however no associated increased risk in contracting the virus (89). A diagnosis of OSA was associated with poor composite COVID-19 outcomes, including severe infection, ICU admission, mechanical ventilation, and death [OR =1.72 (95% CI: 1.55–1.91)] in a meta-analysis reviewing 21 studies and over 50,000 patients with COVID-19 (90).

In contrast, two retrospective studies evaluating OSA and COVID-19 in hospitalized patients did not reveal an independent association between OSA and poor COVID-19 outcomes. One study by Mashaqi *et al.* (91), revealed statistical significance in ICU admission and trend toward statistical significance in length of stay for patients with OSA, however was no longer present when adjusted for age, sex, BMI, and comorbid disease. A second study by Cade *et al.* (92), similarly showed OSA was associated with a greater risk of overall mortality, however after adjusting for demographics, BMI, and comorbidities, the risk of intubation, ICU admission, and inpatient admission was not significant.

Obesity

Obesity, although not traditionally thought of as a respiratory disorder, is known to have effects on both gas exchange (7) as well as mechanical aspects (8) of respiration. In addition, obesity plays a significant role in the morbidity of those with pulmonary disease, as it is known to be a risk factor and disease modifier for a number of pulmonary conditions in addition to predisposing those afflicted with higher rates of respiratory infections and hospitalizations when compared to their non-obese counterparts (93). Here, we aim to review the effect of obesity on pulmonary physiology as it relates to clinical outcomes in COVID-19.

Body mass index (BMI) is used as a measure to classify obesity, as it takes into account height as well as weight, however the pathophysiological consequences related to obesity are closely related to distribution of fat in addition to the magnitude of obesity (94). Central (also known as abdominal or android) obesity, characterized by "apple-shaped" phenotype, with increased fat deposition in the abdomen, thorax, and visceral organs has more direct effects on lung mechanics when compared to peripheral obesity or "pear-shaped" phenotype (95,96).

Adipose deposits in the mediastinum and abdominal cavities alter lung and chest wall mechanics in obese individuals, impeding movement of the diaphragm and chest wall (97,98), resulting in decreased compliance of the respiratory system (99,100). In terms of lung function, this translates into significant decreases in expiratory reserve volume (101) and functional residual capacity (FRC) (102,103), with FRC decreasing proportionally to the degree of obesity (8).

In addition to the mechanical effects of obesity on lung function, there is also alteration in distribution of ventilation, resulting in ventilation/perfusion (V/Q) mismatch (7). In upright, seated individuals, perfusion is greater in the lower lung zones due to effects of gravity, however, it has been shown that ventilation is preferentially distributed to the upper lung zones in obese patients (104). This can be explained by the observation that if FRC is decreased to volumes similar to residual volume (RV), the lower lung zones are not well-ventilated, as is the case in obesity (8,101,105). During normal tidal breathing, this V/Q mismatch results in reduced arterial PO_2 and elevated arterial-alveolar PO_2 gradient in severely obese individuals (7).

These baseline effects on respiration are additive when taking into account the inflammatory and thrombotic sequelae associated with obesity in COVID-19.

Obesity has a significant impact on the immune system, namely the pro-inflammatory state created by the inappropriate production of adipokines and cytokines such as TNF, C-reactive protein (CRP), and IL-6 by adipocytes (106,107). IL-6 has been shown to be an independent risk factor for severe COVID-19 in a prior study (108), with adipose tissue being the primary source of IL-6 production (109). IL-6 has also been shown to be liable for the activation of multiple cytokine pathways (110), propagating a pro-inflammatory state by recruitment of various immune cells (macrophages, T-cells, B-cells) leading to an imbalance and impairing the immune system (106). In the setting of viral infection, such as COVID-19, this pro-inflammatory cytokine production is further amplified, leading to cytokine storm and subsequent deleterious effects such as vascular hyperpermeability, acute respiratory

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distress syndrome (ARDS) and multi-system organ failure seen in severe COVID-19 (111,112).

Obesity itself is known to be associated with a prothrombotic state (113) and together with the effects of venous stasis, translates into an increased risk of venous thromboembolism (VTE) (114). COVID-19 has also been shown to increase risk of VTE as well as disseminated intravascular coagulation, with the risk being proportional to severity of COVID-19 (115).

As it relates to clinical outcomes in COVID-19, current evidence supports that obesity should be considered an independent risk factor for severity of COVID-19. Retrospective studies from multiple centers in China, France, and US have shown obesity increases COVID-19 severity as well as risk of mechanical ventilation, with risk increasing proportional to degree of obesity (38,116-118). A recent meta-analysis and review illustrated that obesity (BMI $\geq$30 kg/m^2) was associated with poor clinical outcomes [OR =1.3 (1.2–1.4)], increased risk of mechanical ventilation [OR =2.1 (1.4–2.7)], and increased mortality [OR =1.35 (1.24–1.460)], but was not associated with increased ICU admission (119) in patients with COVID-19.

Conclusions

In summary, SARS-CoV-2 has many direct and indirect effects within the respiratory system and knowledge of these effects is especially important when managing and counseling patients with underlying respiratory conditions, such as those mentioned in this article. Special consideration should be given to patients with COPD, ILD, and obesity given association with worse clinical outcomes. Data regarding associations with OSA and COVID-19 are limited and conflicting given difficulty in accounting for the shared co-morbidities associated with COVID-19 and OSA. Surprisingly, and in contrast to previously studied viral illnesses, mild to moderate, well-controlled asthma does not carry any increase in associated risk of acquiring COVID-19 or worse clinical outcomes. Understanding the pathophysiologic mechanisms by which COVID-19 affects pulmonary physiology will allow the clinician to make more informed decisions regarding management as well as predicting outcomes in patients with underlying respiratory disease.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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