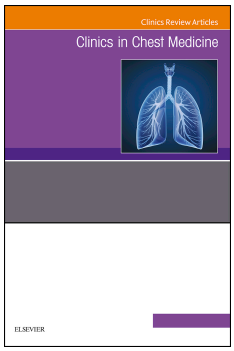
Journal Pre-proof



COVID-19 in patients with chronic lung disease

J.F. Calver, L. Fabbri, J. May, R.G. Jenkins

PII: S0272-5231(22)00129-0

DOI: https://doi.org/10.1016/j.ccm.2022.11.013

Reference: CME 1409

To appear in: *CLINICS IN CHEST MEDICINE*

Please cite this article as: Calver J, Fabbri L, May J, Jenkins R, COVID-19 in patients with chronic lung disease, *CLINICS IN CHEST MEDICINE* (2022), doi: https://doi.org/10.1016/j.ccm.2022.11.013.

COVID-19 in patients with chronic lung disease

Calver, JF., Fabbri, L., May, J., Jenkins RG*.

*RG Jenkins Corresponding Author

Professor R Gisli Jenkins, MD PhD FRCP FERS

National Heart and Lung Institute,

Imperial College London,

Guy Scadding Building,

Cale Street,

London, SW3 6LY

Gisli.jenkins@imperial.ac.uk

Jessica Fae Calver, BSc (Hons)

University of Nottingham

Medical School

Nottingham

NG7 2UH

jessica.calver@nottingham.ac.uk

Laura Fabbri, MD

National Heart and Lung Institute,

Imperial College London,

Guy Scadding Building,

Cale Street,

London, SW3 6LY

l.fabbri@imperial.ac.uk

James May, BSc (Hons) MBBS MRCP

Guy's and St Thomas' NHS Trust

Westminster Bridge

SE1 7EH

james.may4@nhs.net

The authors have nothing to disclose.

Keywords

COVID-19, chronic lung disease, asthma, COPD, cystic fibrosis, interstitial lung disease, pulmonary arterial hypertension, COVID-19 susceptibility, vaccination.

Key Points:

SARS-CoV-2 infection targets the respiratory epithelium.

Patients with Chronic Lung Disease are at risk of more severe COVID-19.

Patients with Chronic Lung Disease should continue with standard therapy, although patients receiving immunosuppression, particularly rituximab, are at higher risk of infection and severe disease.

Patients with Chronic Lung Disease do not appear at higher risk of adverse vaccine reactions and therefore should be offered vaccination which reduces the chance of severe COVID-19.

Abstract

SARS-CoV-2 is a novel coronavirus that causes an acute respiratory tract infection known as COVID-19. SARS-CoV-2 enters cells by binding the ACE2 receptor and co-receptors notably TMPRSS2 or Cathepsin L. Severe COVID-19 infection can lead to Acute Lung Injury (ALI). The pathogenesis of ALI can either be via direct cytopathogenesis secondary to infection or indirectly via immune mediated epithelial injury. Chronic lung disease may alter susceptibility, and response, to SARS-CoV-2 infection, similarly therapies used to treat CLD will impact on infection and ultimately determine the nature and severity of COVID-19. Below we describe the current evidence of the impact of common CLDs on the development of COVID-19. The impact of treatment of CLD on COVID-19 and any risk of vaccination in patients with CLD are considered.

Main text

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that leads to an acute respiratory tract infection and for the first couple of years of the pandemic lead to acute lung injury in a substantial proportion of people. The combination of improved therapy, vaccination, and mutant strains with a lower trophism for alveolar epithelium appear to have reduced the number of people overall with severe respiratory complications of severe coronavirus disease 2019 (COVID-19). However, patients with a pre-existing chronic lung disease (CLD) may have an increased risk of acquiring SARS-CoV-2 infection and also have an increased risk of COVID-19 following with poor outcomes.[1-3] It is therefore crucial to understand the interaction between SARS-CoV-2 and the respiratory tract, especially in patients with compromised pulmonary physiology, to understand the pathogenesis of severe COVID-19 and complications such as 'long COVID'.

Mechanisms of SARS-CoV-2 Infection in the Lung

Severe COVID-19 has been associated with SARS-CoV-2 infection of the lower respiratory tract with the primary site of infection being type II alveolar epithelial cells (AT2) in the distal lung.[4] Early in February 2020, it was reported that the major mechanism for SARS-CoV-2 viral entry into cells was via angiotensin-converting enzyme 2 (ACE2) expressed on the cell surface.[5] Yet, single-cell RNA-sequencing (scRNAseq) and protein atlas assessment of ACE2 determined low ACE2 gene expression and rare ACE2 protein expression in the airway epithelium and alveoli of control and CLD groups.[4,6] The low level of ACE2 expression at the major site of infection within the lungs suggests that it is likely that alternative non-ACE2 mediated mechanisms of cell infection exist in the lung and that these might be responsible for the worse outcomes of CLD patients. The virus has been shown to utilise several co-receptors including CD147/Basigin/BSG, NRP1, GRP78/HSPA5 and proteases TMPRSS2, Cathepsin L/CTSL, FURIN, ADAM17 to facilitate infection.[1,4,7-13] Difference in these co-receptors explain the different pathogenicity of the newer Omicron variants[14], however, the overall differences in SARS-CoV-2 entry factors are minimal in CLD, suggesting that viral entry alone does not explain the variation

in disease severity observed between patients with and without CLD.[4] More recently, it has been hypothesised that in addition to increased susceptibility to infection, CLD patients have altered expression profiles of anti-viral and immune response genes, altering their alveolar microenvironment and ability to fight infection. Having impaired innate immunity reduces the antiviral defence which may promote host permissiveness and an increase in viral replication. As a result, they may be predisposed to severe lung injury.[4]

Although CLD has been cited as a risk factor for severe COVID-19, the different types of CLD have distinct pathological mechanisms and treatment modalities. Subsequently, the molecular characteristics influencing SARS-CoV-2 severity differ between the groups.

Asthma

Asthma is an inflammatory condition of the airways occurring in all age groups but is more common in younger patients and is commonly associated with allergic diseases such as rhinosinusitis. Exacerbations of asthma are frequently caused by viral infections including rhinovirus and influenza and may be life-threatening. Asthma patients have impaired type-I interferon (IFN-I) responses, yet the risk of severe COVID-19 differs between the two main asthma endotypes: type-2 (allergic and eosinophilic) vs non-type-2 (neutrophilic and paucigranulocytic).[15]

In type-2 asthma, the pro-inflammatory cytokines IL-4, IL-5 and IL-13 are secreted to drive a Th2-type immune response, which perhaps modulates SARS-CoV-2 infectivity with IL-13 shown to downregulate ACE2 expression by airway epithelial cells (AECs).[16-18] In addition, type-2 cytokines and IgE crosslinking have previously been shown to suppress toll-like receptor (TLR) expression, possibly preventing an IFN-driven upregulation of ACE2.[19,20] Yet IL-13 increases TMPRSS2 expression, although a low frequency of dual ACE2+/TMPRSS2+ expressing cells are present for viral entry.[18] It has been suggested that the preventative inhaled corticosteroid (ICS), ciclesonide, may even have inhibitory effects on viral replication by binding to the SARS-CoV-2 viral endonuclease NSP15.[21,22] In a

randomised trial, patients treated with ciclesonide had reduced hospital attendance, although symptom duration was not reduced.[23] Additional protective factors in type-2 asthma patients include eosinophilia contributing to antiviral immunity and pre-existing ICS usage for the long-term management of asthma.[24] Pre-existing eosinophilia (>150 cells/μL) was protective against hospital admission and the development of eosinophilia during admission was protective against mortality.[25] Consequently, concerns are raised regarding the use of biologic agents which directly interfere with Th2 inflammation and eosinophil function, yet their use is lifesaving in those with the worst forms of asthma. Reassuringly, a large cohort study did not find higher prevalence or worse outcomes in asthma patients on biologic therapy.[26]

By comparison, it has been suggested that individuals with non-type-2 asthma have an increased risk of severe COVID-19. In non-type-2 asthma, there is a greater involvement of Th1 and Th17 responses, predominantly via the cytokines IL-1β, IL-8, IL-6 and IL-17, many of which play a central role in the 'cytokine storm'.[15] Non-type-2 cytokines have been associated with an increased expression of ACE2 in epithelial cells, which may increase SARS-CoV-2 infection and similarly these individuals have low eosinophil levels which usually have a protective role in viral infection.[27] Adding to this, IL-17 induces neutrophil migration during asthma onset and these neutrophil levels (%) have been shown to significantly associate with FURIN gene expression in sputum.[28]

The different responses of eosinophilic and neutrophilic phenotypes may be the cause of conflicting data from studies of asthmatic patient. Early large-scale studies concluded that there was a higher incidence of COVID-19 in patients with asthma, that there was a higher risk of severe COVID-19 (although asthma was not an independent risk factor) and that asthma treatment including biologic therapy did not influence disease course.[29,30] However, a more recent meta-analysis found that the risk of contracting COVID-19 was lower in patients with asthma versus non-asthmatics and importantly there were no significant differences in hospitalisation, intensive care admission or mechanical

ventilation requirements.[31] Although once intubated, asthma patients are more likely to require longer periods of mechanical ventilation which has been identified as an independent risk factor.[32]

Few cases of asthma exacerbation after COVID-19 vaccination have been reported.[33] However, the overall benefit of vaccination against SARS-CoV-2 outweighs the extremely low overall risk of an allergic reaction should not discourage the vaccination.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease characterised by airway inflammation and alveolar destruction.[34] Expiratory airflow limitation with an FEV1/FVC ratio of less than 0.7 is diagnostic and the condition is associated with former smoking, current smoking or noxious fume exposure. Pharmacotherapy includes bronchodilators and in certain cases ICS.[35] Acute exacerbations of COPD are characterised by worsening symptoms relative to the stable state which frequently cause hospitalisation and lung function deterioration in this patient group. An exacerbation is commonly triggered by infection, particularly viruses.[36] Subsequently, the emergence of SARS-CoV-2 raised concerns about the deleterious impact COVID-19 may have on the 'clinically extremely vulnerable' COPD patients with an increased risk of mortality.[37-39] COPD patients are at higher risk of hospitalisation and have four-fold higher risk of developing severe COVID-19.[38,40]

COPD patients have dampened IFN-I responses which may consequently increase the risk of SARS-CoV-2 infection in the airway epithelium.[41] Recent evidence has implicated a reduction in expression of the pattern recognition receptors (PRRs) retinoic acid-inducible gene I (RIG-I)-like receptors and melanoma differentiation-associated protein 5 (MDA-5).[41] These PRRs are a part of the innate immunity defence and recognise pathogen-associated molecular patterns (PAMPs) and/or damage-associated molecular patterns (DAMPs) to induce an anti-viral IFN-I response. In addition, expression of the type-I interferon IFN-β and its transcription factor IRF-7 are also decreased in COPD patients.[41,42] In contrast, TLR2 and TLR4 expression is increased in COPD patients which may be driving

inflammation and an IFN-driven upregulation of the Interferon-stimulated gene (ISG) ACE2.[42-44] Alongside the dysregulation of these immune factors, TMPRSS2 protein expression is upregulated in COPD lung homogenates and NRP1 expression slightly upregulated in COPD macrophages.[4,45] Whether ACE2, CD147 and FURIN are upregulated in COPD to facilitate viral entry remains to be determined.[4,6,45-49]

To date, the overall prevalence of COVID-19 does not appear to be increased in COPD patients. The impact of smoking on COVID-19 outcomes remains a topic of debate, although never smokers are likely to have better outcomes than current or former smokers.[39] There are several factors which may increase the risk of severe disease with poor outcomes in COPD patients. Impaired lung function including air flow limitation, hyperinflation with poor inspiratory reserve, reduced gas transfer and impaired host defence blunt the ability to compensate for the vast pathology which affects the lungs in COVID-19 pneumonitis (inflammatory infiltrates, interstitial oedema progressing to ARDS, and thromboembolism/in situ thrombosis).[50,51]

Like asthma, COPD patients have continued with their established management therapies and have not adjusted, withdrawn or escalated treatment during the COVID-19 pandemic. No harm has been reported with inhaled bronchodilator therapy although ICS is a more contentious issue. It has been demonstrated by *in vivo* and *in vitro* studies that ICS attenuate ACE2 receptor expression, yet a large cohort of COPD patients receiving ICS were reported to be at increased risk of death from COVID-19 compared to those on LABA/LAMA therapy.[52,53] However, there was likely significant unmeasured confounding from disease severity, given that most patients on ICS tend to experience frequent exacerbations and/or have more severe airflow obstruction. The consensus is that inhaled treatment should be continued unaltered in stable patients.[54]

Initially, concerns were raised regarding the management of COPD acute exacerbations with oral corticosteroids. Early in the pandemic there was significant anxiety over their use, especially given previous data from the Middle East respiratory syndrome coronavirus (MERS-CoV) pandemic.[55] This

has now been superseded by the findings of the RECOVERY trial which demonstrated a mortality benefit of dexamethasone for all patients requiring supplemental oxygen therapy; this is now accepted standard of care for severe COVID-19.[56] Surprisingly, there has been a 50% reduction in hospital admission from COPD exacerbations in pre-pandemic vs pandemic times. This is likely reflective of patients isolating from the general public resulting in reduced viral transmission (not limited to SARS-CoV-2). Although these observations may guide important public health strategy, significant depression and anxiety associated with social isolation is likely to result.[57] There is currently no evidence of an adverse effect of COVID-19 vaccines in COPD patients, nor diminished efficacy.

Bronchiectasis

Bronchiectasis is a condition of abnormally dilatated airways and impaired mucociliary clearance. There are various causes including genetic (cystic fibrosis and primary ciliary dyskinesia), post-infectious (bacterial pneumonia, whooping cough and tuberculosis), autoimmune (rheumatoid arthritis and inflammatory bowel disease) and immune dysfunction. The architectural distortion of the airways causes chronic sputum production and increased susceptibility to pulmonary infection. In comparison with some other forms of CLD, bronchiectasis patients have a higher risk of contracting COVID-19, more severe disease, and poorer outcomes.[58] This may relate to the structural pulmonary abnormalities and impaired host defence response causing a greater risk of infection and respiratory failure. Corticosteroid treatments (inhaled or oral) are less commonly used in the chronic management of bronchiectasis or exacerbation management compared to asthma and COPD. Similar to patients with COPD and cystic fibrosis (CF), studies demonstrate a significant decrease in the frequency of reported exacerbations during the COVID pandemic.[59]

Cystic Fibrosis

CF is an autosomal recessive disease affecting the lungs, digestive system, sweat glands and reproductive tract. The primary abnormality is in chloride and sodium transport across secretory

epithelia causing thickened viscous secretions in the bronchi, biliary tract, pancreas, intestines and reproductive system. Although the disease is systemic, progressive lung disease continues to be the major cause of morbidity and mortality for most patients.[60] The thick airway secretions cause chronic airway obstruction which gets progressively colonised by pathogenic bacteria. Once infection is established, neutrophils are unable to control the bacteria and release elastase which overwhelms the antiproteases of the lung and contributes to tissue destruction.[61] In addition, large amounts of DNA and cytosol matrix proteins are released by degranulating neutrophils, contributing to the increased viscosity of the airway mucus. Chronic infection and an ineffective inflammatory response appear to be the major stimulus for an exuberant which subsequently results in bronchiectasis.[62,63]

Although the sputum levels of IL-6 are lower in patients with CF which may protect against severe COVID-19, CF patients are still categorised as a high-risk group.[64] ACE2 messenger RNA (mRNA) is elevated in CF airway epithelial cells when compared to non-CF cells, but TMPRSS2 mRNA levels are decreased.[65] CF cells also display elevated FURIN activity which has been shown to increase TGF-β1 production.[66] Cystic fibrosis transmembrane conductance regulator (CFTR) modulators administered for CF treatment are thought to be protective against severe COVID-19.[67]

To date, the literature suggests that CF individuals appear to be contracting SARS-CoV-2 viral infection at a lower rate compared to the general population. Lower rates of SARS-CoV-2 infection in CF individuals are likely explained by the increased awareness of infection, prevention and control practices including frequent hand hygiene, mask wearing and continued social distancing. Although the hospitalisation rates are higher in CF than in the general population, individuals with CF appear to have better outcomes than initially anticipated, when compared with other respiratory viral infections. There are no specific concerns regarding the safety of mRNA vaccines in CF patients. A small cohort study showed that CF patients mounted sufficient antibody responses after immunisation irrelevant of CFTR genotype, related comorbidities, or treatment type.[68]

Interstitial Lung Disease

The term Interstitial lung disease (ILD) encompasses a group of respiratory diseases affecting the alveolar parenchyma, with inflammation and/or fibrosis affecting the alveolar interstitium. These alterations cause increased morbidity and mortality. ILDs can have a known aetiology such as occupational exposure to mould, metals, chemical substances or drugs and autoimmune diseases. However, a large number of ILDs have no known cause with Idiopathic pulmonary fibrosis (IPF) being the most well studied.[69]

ILD patients have an increased frequency of COVID-19 infection compared with the general population, however, COVID-19 susceptibility differs among the ILD subtypes. The incidence of COVID-19 is higher in IPF patients, however, patients with sarcoidosis and chronic hypersensitivity pneumonitis do not show increased susceptibility to the disease.[70-73] In addition to increased susceptibility, ILD patients have more severe disease than those without ILD. After COVID-19 infection they require more oxygen therapy, intensive care admission and mechanical ventilation.[73]

In IPF there is an increase in ACE2 protein expression, specifically in the small airways.[4] There are also significantly lower plasma levels of soluble ACE2 in pulmonary fibrosis patients which normally acts as a decoy protein to neutralise SARS-CoV-2 infectivity.[45] This regional increase in ACE2+ cells in the distal lung alongside an upregulation of the epithelial-restricted αvβ6 integrin in AT2 cells, may explain the increased severity in IPF patients despite overall low ACE2 expression levels.[4] The integrin αvβ6 is critical in the pathogenesis of IPF and is upregulated in the fibrotic regions of an IPF lung.[74] The Arg-Gly-Asp (RGD) binding integrin was suggested as a co-receptor for SARS-CoV-2 infectivity as unlike any other coronavirus, the SARS-CoV-2 spike protein has acquired an RGD motif.[75] The SARS-CoV-2 spike protein S1 subunit can bind to αvβ6, and its overexpression has been shown to augment ACE2-dependent SARS-CoV-2 pseudoviral entry into epithelial cells. The αvβ6 integrin also mediates TGF-β1 activation in human epithelial cells and this enhanced TGF-β1 signalling can supress anti-viral IFN-I signalling activity by alveolar macrophages.[74,76-78] This may explain the increased severity in IPF

patients despite overall low ACE2 expression levels. A positive correlation between NRP1 and FURIN expression also exists in IPF AT2 cells which may facilitate viral entry.[4] The MUC5B promoter rs35705950T allele is a genetic risk factor for IPF development and has additionally been associated with COVID-19 but appears to be protective against severe disease, perhaps because MUC5B forms part of the innate immune response.[79] The two anti-fibrotic therapies approved for IPF treatment, nintedanib and pirfenidone, may also protect against severe COVID-19 by attenuating pro-fibrotic pathways and IL-6 cytokine levels.[4] Yet short telomere length is a risk factor for both familial and sporadic IPF and has been shown to be associated with increased COVID-19 infection and disease severity.[80]

Studies have suggested that COVID-19 vaccines may be less effective in immunocompromised patients, who are at increased risk of severe COVID-19.[81] Particularly, those with autoimmune diseases and associated ILDs may fail to mount the desired antibody response with mRNA vaccinations.[82] The lower responses correlated with coexistent ongoing treatments, particularly glucocorticoids, mycophenolate mofetil and rituximab.[83] Similarly, patients with IPF did not mount expected anti-spike antibody responses to two doses of SARS-CoV-2 mRNA, irrespective of current antifibrotic treatment.[84] Anecdotally, acute exacerbation of IPF have been reported after vaccine administration in people with ILD related autoimmune diseases and IPF. These episodes might suggest that the immune response induced by the vaccine may activate a pathobiological cascades leading to the acute exacerbation in susceptible patients. Still, vaccine associated exacerbation should be considered a rare event occurring in a small minority of vaccinated IPF patients.[83,85,86] These cases do however raise an important question which can only be answered by larger, prospective studies comparing the rate of ILD exacerbations between vaccinated and unvaccinated groups.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a vasculopathy characterised by remodelling and thickening of the pulmonary arteries with increased vascular resistance and right heart dysfunction. Early in the

COVID-19 pandemic, there was a suggestion that patients with PAH may be protected from severe COVID-19.[87] Successively, large cohort studies showed that cumulative incidence was similar to the general population, however outcomes were worse with half of patients requiring hospitalisation and a 12% rate of mortality.[88]

A possible pathogenic mechanism explaining these findings is the reduction of ACE2 in patients with PAH.[89] This downregulation leads to higher circulating levels of angiotensin II with worsened ensuing lung.[90] PAH specific therapies including the endothelin receptor antagonists and phosphodiesterase type 5 inhibitors, are also very likely to be important. Endothelin I stabilises ACE2 expression which may both enhance viral binding and replication but also protect against high expression of angiotensin II. Similarly, some of these agents may have anti-inflammatory and antithrombotic properties. However, most importantly their vasodilatory effect may worsen V:Q mismatch by enhancing blood flow to poor ventilated areas of lung and worsening hypoxaemia.[91]

It is recommended that established PAH therapy is continued unchanged in the face of infection with COVID-19. However, this patient group may display a more challenging management approach regarding oxygen and ventilatory support. Positive-pressure ventilation (including high flow nasal oxygen, continuous positive airway pressure, and bi-level positive airway pressure) is often used to manage severe hypoxaemia, as a bridge or to delay intubation. However, increased airway pressure from these modalities may decrease venous return to the right ventricle and worsen the already struggling cardiopulmonary haemodynamic, making these patients unstable. Similarly, invasive ventilation requires general anaesthesia to manage an anticipated reduction in vascular tone and worsening right heart failure. In these situations, patients may require vasopressor support which presents its own challenges.[92] No evidence of contraindication of COVID-19 vaccines in patients with pulmonary hypertension have been reported, nor is there evidence of diminished vaccine efficacy in this group of patients.

Summary

In summary, the presence of some pre-existing CLD may increase the risk of contracting COVID-19, which frequently leads to worse outcomes including increased disease severity and mortality. However, the baseline health status and comorbidities also influence the evolution of COVID-19 and these need to be evaluated in the context of CLD. No evidence currently supports the change of chronic therapy, nor is there convincing evidence of an increased risk of adverse reaction to COVID-19 vaccination thus vaccine uptake should be encouraged. There continues to be a considerable health burden of COVID-19 in patients with CLD, and health care policy should prioritise the use of anti-viral therapies in these vulnerable patients.

Clinics Care Points

References

1. Halpin DMG, Faner R, Sibila O, Badia JR, Agusti A. Do chronic respiratory diseases or their treatment affect the risk of SARS-CoV-2 infection? *Lancet Respiratory Medicine.* 2020;8(5):436-438.

2. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. *Lancet Respir Med.* 2020;8(8):807-815.

3. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature.* 2020;584(7821):430-436.

4. Bui LT, Winters NI, Chung MI, et al. Chronic lung diseases are associated with gene expression programs favoring SARS-CoV-2 entry and severity. *Nat Commun.* 2021;12(1):4314.

5. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* 2020;579(7798):270-273.

6. Aguiar JA, Tremblay BJ, Mansfield MJ, et al. Gene expression and in situ protein profiling of candidate SARS-CoV-2 receptors in human airway epithelial cells and lung tissue. *Eur Respir J.* 2020;56(3).

7. Cantuti-Castelvetri L, Ojha R, Pedro LD, et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. *Science.* 2020;370(6518):856-860.

8. Carlos AJ, Ha DP, Yeh DW, et al. The chaperone GRP78 is a host auxiliary factor for SARS-CoV-2 and GRP78 depleting antibody blocks viral entry and infection. *J Biol Chem.* 2021;296:100759.

9. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell.* 2020;181(2):271-280 e278.

10. Ibrahim IM, Abdelmalek DH, Elshahat ME, Elfiky AA. COVID-19 spike-host cell receptor GRP78 binding site prediction. *J Infect.* 2020;80(5):554-562.

11. Ou X, Liu Y, Lei X, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nat Commun.* 2020;11(1):1620.

12. Wang K, Chen W, Zhang Z, et al. CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. *Signal Transduct Target Ther.* 2020;5(1):283.

13. Zhao MM, Yang WL, Yang FY, et al. Cathepsin L plays a key role in SARS-CoV-2 infection in humans and humanized mice and is a promising target for new drug development. *Signal Transduct Target Ther.* 2021;6(1):134.

14. Zhang Y-N, Zhang Z-R, Zhang H-Q, et al. Different pathogenesis of SARS-CoV-2 Omicron variant in wild-type laboratory mice and hamsters. *Signal Transduction and Targeted Therapy.* 2022;7(1):62.

15. Lombardi C, Gani F, Berti A, Comberiati P, Peroni D, Cottini M. Asthma and COVID-19: a dangerous liaison? *Asthma Res Pract.* 2021;7(1):9.

16. Jackson DJ, Busse WW, Bacharier LB, et al. Association of respiratory allergy, asthma, and expression of the SARS-CoV-2 receptor ACE2. *J Allergy Clin Immunol.* 2020;146(1):203-206 e203.

17. Kimura H, Francisco D, Conway M, et al. Type 2 inflammation modulates ACE2 and TMPRSS2 in airway epithelial cells. *J Allergy Clin Immunol.* 2020;146(1):80-88 e88.

18. Sajuthi SP, DeFord P, Li Y, et al. Type 2 and interferon inflammation regulate SARS-CoV-2 entry factor expression in the airway epithelium. *Nat Commun.* 2020;11(1):5139.

19. Contoli M, Ito K, Padovani A, et al. Th2 cytokines impair innate immune responses to rhinovirus in respiratory epithelial cells. *Allergy.* 2015;70(8):910-920.

20. Gill MA, Bajwa G, George TA, et al. Counterregulation between the FcepsilonRI pathway and antiviral responses in human plasmacytoid dendritic cells. *J Immunol.* 2010;184(11):5999-6006.

21. Kimura H, Kurusu H, Sada M, et al. Molecular pharmacology of ciclesonide against SARS-CoV-2. *J Allergy Clin Immunol.* 2020;146(2):330-331.

22. Matsuyama S, Kawase M, Nao N, et al. The Inhaled Steroid Ciclesonide Blocks SARS-CoV-2 RNA Replication by Targeting the Viral Replication-Transcription Complex in Cultured Cells. *J Virol.* 2020;95(1).

23. Clemency BM, Varughese R, Gonzalez-Rojas Y, et al. Efficacy of Inhaled Ciclesonide for Outpatient Treatment of Adolescents and Adults With Symptomatic COVID-19: A Randomized Clinical Trial. *JAMA Intern Med.* 2022;182(1):42-49.

24. Padayachee Y, Faiez TS, Singanayagam A, Mallia P, Johnston SL. Asthma and viruses: A focus on rhinoviruses and SARS-CoV-2. *J Allergy Clin Immunol.* 2021;147(5):1648-1651.

25. Ferastraoaru D, Hudes G, Jerschow E, et al. Eosinophilia in Asthma Patients Is Protective Against Severe COVID-19 Illness. *J Allergy Clin Immunol Pract.* 2021;9(3):1152-1162 e1153.

26. Matucci A, Caminati M, Vivarelli E, et al. COVID-19 in severe asthmatic patients during ongoing treatment with biologicals targeting type 2 inflammation: Results from a multicenter Italian survey. *Allergy.* 2021;76(3):871-874.

27. Camiolo M, Gauthier M, Kaminski N, Ray A, Wenzel SE. Expression of SARS-CoV-2 receptor ACE2 and coincident host response signature varies by asthma inflammatory phenotype. *J Allergy Clin Immunol.* 2020;146(2):315-324 e317.

28. Kermani NZ, Song WJ, Badi Y, et al. Sputum ACE2, TMPRSS2 and FURIN gene expression in severe neutrophilic asthma. *Respir Res.* 2021;22(1):10.

29. Choi YJ, Park JY, Lee HS, et al. Effect of asthma and asthma medication on the prognosis of patients with COVID-19. *Eur Respir J.* 2021;57(3).

30. Izquierdo JL, Almonacid C, Gonzalez Y, et al. The impact of COVID-19 on patients with asthma. *Eur Respir J.* 2021;57(3).

31. Sunjaya AP, Allida SM, Di Tanna GL, Jenkins CR. Asthma and COVID-19 risk: a systematic review and meta-analysis. *Eur Respir J.* 2022;59(3).

32. Mahdavinia M, Foster KJ, Jauregui E, et al. Asthma prolongs intubation in COVID-19. *J Allergy Clin Immunol Pract.* 2020;8(7):2388-2391.

33. Colaneri M, De Filippo M, Licari A, et al. COVID vaccination and asthma exacerbation: might there be a link? *Int J Infect Dis.* 2021;112:243-246.

34. Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan I. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis. *The Lancet Respiratory Medicine.* 2022;10(5):447-458.

35. Gupta N, Malhotra N, Ish P. GOLD 2021 guidelines for COPD - what's new and why. *Adv Respir Med.* 2021;89(3):344-346.

36. Wedzicha JA, Singh R, Mackay AJ. Acute COPD exacerbations. *Clin Chest Med.* 2014;35(1):157-163.

37. Gerayeli FV, Milne S, Cheung C, et al. COPD and the risk of poor outcomes in COVID-19: A systematic review and meta-analysis. *EClinicalMedicine.* 2021;33:100789.

38. Lacedonia D, Scioscia G, Santomasi C, et al. Impact of smoking, COPD and comorbidities on the mortality of COVID-19 patients. *Sci Rep.* 2021;11(1):19251.

39. Patanavanich R, Glantz SA. Smoking Is Associated With COVID-19 Progression: A Meta-analysis. *Nicotine Tob Res.* 2020;22(9):1653-1656.

40. Zhao Q, Meng M, Kumar R, et al. The impact of COPD and smoking history on the severity of COVID-19: A systemic review and meta-analysis. *J Med Virol.* 2020;92(10):1915-1921.

41. Garcia-Valero J, Olloquequi J, Montes JF, et al. Deficient pulmonary IFN-beta expression in COPD patients. *PLoS One.* 2019;14(6):e0217803.

42. Guo-Parke H, Linden D, Weldon S, Kidney JC, Taggart CC. Deciphering Respiratory-Virus-Associated Interferon Signaling in COPD Airway Epithelium. *Medicina (Kaunas).* 2022;58(1).

43. Hansbro PM, Haw TJ, Starkey MR, Miyake K. Toll-like receptors in COPD. *Eur Respir J.* 2017;49(5).

44. Ziegler CGK, Allon SJ, Nyquist SK, et al. SARS-CoV-2 Receptor ACE2 Is an Interferon-Stimulated Gene in Human Airway Epithelial Cells and Is Detected in Specific Cell Subsets across Tissues. *Cell.* 2020;181(5):1016-1035 e1019.

45. Fliesser E, Birnhuber A, Marsh LM, et al. Dysbalance of ACE2 levels - a possible cause for severe COVID-19 outcome in COPD. *J Pathol Clin Res.* 2021;7(5):446-458.

46. Saheb Sharif-Askari N, Saheb Sharif-Askari F, Alabed M, et al. Airways Expression of SARS-CoV-2 Receptor, ACE2, and TMPRSS2 Is Lower in Children Than Adults and Increases with Smoking and COPD. *Mol Ther Methods Clin Dev.* 2020;18:1-6.

47. Maremanda KP, Sundar IK, Li D, Rahman I. Age-Dependent Assessment of Genes Involved in Cellular Senescence, Telomere, and Mitochondrial Pathways in Human Lung Tissue of Smokers, COPD, and IPF: Associations With SARS-CoV-2 COVID-19 ACE2-TMPRSS2-Furin-DPP4 Axis. *Front Pharmacol.* 2020;11:584637.

48. Radzikowska U, Ding M, Tan G, et al. Distribution of ACE2, CD147, CD26, and other SARS-CoV-2 associated molecules in tissues and immune cells in health and in asthma, COPD, obesity, hypertension, and COVID-19 risk factors. *Allergy.* 2020;75(11):2829-2845.

49. Aloufi N, Traboulsi H, Ding J, et al. Angiotensin-converting enzyme 2 expression in COPD and IPF fibroblasts: the forgotten cell in COVID-19. *Am J Physiol Lung Cell Mol Physiol.* 2021;320(1):L152-L157.

50. Hu W, Dong M, Xiong M, et al. Clinical Courses and Outcomes of Patients with Chronic Obstructive Pulmonary Disease During the COVID-19 Epidemic in Hubei, China. *Int J Chron Obstruct Pulmon Dis.* 2020;15:2237-2248.

51. Thomas M, Price OJ, Hull JH. Pulmonary function and COVID-19. *Curr Opin Physiol.* 2021;21:29-35.

52. Finney LJ, Glanville N, Farne H, et al. Inhaled corticosteroids downregulate the SARS-CoV-2 receptor ACE2 in COPD through suppression of type I interferon. *J Allergy Clin Immunol.* 2021;147(2):510-519 e515.

53. Schultze A, Walker AJ, MacKenna B, et al. Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an

observational cohort study using the OpenSAFELY platform. *The Lancet Respiratory Medicine.* 2020;8(11):1106-1120.

54. Halpin DMG, Singh D, Hadfield RM. Inhaled corticosteroids and COVID-19: a systematic review and clinical perspective. *Eur Respir J.* 2020;55(5).

55. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. *Am J Respir Crit Care Med.* 2018;197(6):757-767.

56. Group RC, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med.* 2021;384(8):693-704.

57. Alqahtani JS, Oyelade T, Aldhahir AM, et al. Reduction in hospitalised COPD exacerbations during COVID-19: A systematic review and meta-analysis. *PLoS One.* 2021;16(8):e0255659.

58. Choi H, Lee H, Lee SK, et al. Impact of bronchiectasis on susceptibility to and severity of COVID-19: a nationwide cohort study. *Ther Adv Respir Dis.* 2021;15:1753466621995043.

59. Crichton ML, Shoemark A, Chalmers JD. The Impact of the COVID-19 Pandemic on Exacerbations and Symptoms in Bronchiectasis: A Prospective Study. *Am J Respir Crit Care Med.* 2021;204(7):857-859.

60. Guggino WB. Cystic Fibrosis and the Salt Controversy. *Cell.* 1999;96(5):607-610.

61. Griese M, Kappler M, Gaggar A, Hartl D. Inhibition of airway proteases in cystic fibrosis lung disease. *Eur Respir J.* 2008;32(3):783-795.

62. DiMango E, Ratner AJ, Bryan R, Tabibi S, Prince A. Activation of NF-kappaB by adherent Pseudomonas aeruginosa in normal and cystic fibrosis respiratory epithelial cells. *J Clin Invest.* 1998;101(11):2598-2605.

63. Heeckeren A, Walenga R, Konstan MW, Bonfield T, Davis PB, Ferkol T. Excessive inflammatory response of cystic fibrosis mice to bronchopulmonary infection with Pseudomonas aeruginosa. *J Clin Invest.* 1997;100(11):2810-2815.

64. Marcinkiewicz J, Mazurek H, Majka G, Chain B. Are patients with lung cystic fibrosis at increased risk of severe and fatal COVID-19? Interleukin 6 as a predictor of COVID-19 outcomes. *Pol Arch Intern Med.* 2020;130(10):919-920.

65. Stanton BA, Hampton TH, Ashare A. SARS-CoV-2 (COVID-19) and cystic fibrosis. *Am J Physiol Lung Cell Mol Physiol.* 2020;319(3):L408-L415.

66. Ornatowski W, Poschet JF, Perkett E, Taylor-Cousar JL, Deretic V. Elevated furin levels in human cystic fibrosis cells result in hypersusceptibility to exotoxin A-induced cytotoxicity. *J Clin Invest.* 2007;117(11):3489-3497.

67. Peckham D, McDermott MF, Savic S, Mehta A. COVID-19 meets Cystic Fibrosis: for better or worse? *Genes Immun.* 2020;21(4):260-262.

68. Michos A, Filippatos F, Tatsi EB, et al. Immunogenicity of the COVID-19 BNT162b2 vaccine in adolescents and young adults with cystic fibrosis. *J Cyst Fibros.* 2022;21(3):e184-e187.

69. American Thoracic S, European Respiratory S. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med.* 2002;165(2):277-304.

70. Baughman RP, Lower EE, Buchanan M, et al. Risk and outcome of COVID-19 infection in sarcoidosis patients: results of a self-reporting questionnaire. *Sarcoidosis Vasc Diffuse Lung Dis.* 2020;37(4):e2020009.

71. George LJ, Philip AM, John KJ, et al. A review of the presentation and outcome of sarcoidosis in coronavirus disease 2019. *J Clin Transl Res.* 2021;7(5):657-665.

72. Kahlmann V, Manansala M, Moor CC, Shahrara S, Wijsenbeek MS, Sweiss NJ. COVID-19 infection in patients with sarcoidosis: susceptibility and clinical outcomes. *Curr Opin Pulm Med.* 2021;27(5):463-471.

73. Lee H, Choi H, Yang B, et al. Interstitial lung disease increases susceptibility to and severity of COVID-19. *Eur Respir J.* 2021;58(6):2004125.

74. Munger JS, Huang X, Kawakatsu H, et al. A Mechanism for Regulating Pulmonary Inflammation and Fibrosis: The Integrin αvβ6 Binds and Activates Latent TGF β1. *Cell.* 1999;96(3):319-328.

75. Sigrist CJ, Bridge A, Le Mercier P. A potential role for integrins in host cell entry by SARS-CoV-2. *Antiviral Res.* 2020;177:104759.

76. Jenkins RG, Su X, Su G, et al. Ligation of protease-activated receptor 1 enhances alpha(v)beta6 integrin-dependent TGF-beta activation and promotes acute lung injury. *J Clin Invest.* 2006;116(6):1606-1614.

77. Meliopoulos VA, Van de Velde LA, Van de Velde NC, et al. An Epithelial Integrin Regulates the Amplitude of Protective Lung Interferon Responses against Multiple Respiratory Pathogens. *PLoS Pathog.* 2016;12(8):e1005804.

78. Xu MY, Porte J, Knox AJ, et al. Lysophosphatidic acid induces alphavbeta6 integrin-mediated TGF-beta activation via the LPA2 receptor and the small G protein G alpha(q). *Am J Pathol.* 2009;174(4):1264-1279.

79. van Moorsel CHM, van der Vis JJ, Duckworth A, et al. The MUC5B Promoter Polymorphism Associates With Severe COVID-19 in the European Population. *Front Med (Lausanne).* 2021;8:668024.

80. Drake TM, Docherty AB, Harrison EM, et al. Outcome of Hospitalization for COVID-19 in Patients with Interstitial Lung Disease. An International Multicenter Study. *Am J Respir Crit Care Med.* 2020;202(12):1656-1665.

81. Galmiche S, Luong Nguyen LB, Tartour E, et al. Immunological and clinical efficacy of COVID-19 vaccines in immunocompromised populations: a systematic review. *Clin Microbiol Infect.* 2022;28(2):163-177.

82. Furer V, Eviatar T, Zisman D, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. *Ann Rheum Dis.* 2021;80(10):1330-1338.

83. Ferri C, Ursini F, Gragnani L, et al. Impaired immunogenicity to COVID-19 vaccines in autoimmune systemic diseases. High prevalence of non-response in different patients' subgroups. *J Autoimmun.* 2021;125:102744.

84. Karampitsakos T, Papaioannou O, Dimeas I, et al. Reduced immunogenicity of the mRNA vaccine BNT162b2 in patients with idiopathic pulmonary fibrosis. *ERJ Open Res.* 2022;8(2):00082-02022.

85. Sgalla G, Magri T, Lerede M, Comes A, Richeldi L. COVID-19 Vaccine in Patients with Exacerbation of Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med.* 2022;206(2):219-221.

86. Ehteshami-Afshar S, Raj R. COVID-19 mRNA Vaccines and ILD Exacerbation: Causation or Just a Temporal Association? *Am J Respir Crit Care Med.* 2022;0(ja):null.

87. Horn EM, Chakinala M, Oudiz R, Joseloff E, Rosenzweig EB. Could pulmonary arterial hypertension patients be at a lower risk from severe COVID-19? *Pulm Circ.* 2020;10(2):2045894020922799.

88. Lee JD, Burger CD, Delossantos GB, et al. A Survey-based Estimate of COVID-19 Incidence and Outcomes among Patients with Pulmonary Arterial Hypertension or Chronic Thromboembolic Pulmonary Hypertension and Impact on the Process of Care. *Ann Am Thorac Soc.* 2020;17(12):1576-1582.

89. Hemnes AR, Rathinasabapathy A, Austin EA, et al. A potential therapeutic role for angiotensin-converting enzyme 2 in human pulmonary arterial hypertension. *European Respiratory Journal.* 2018;51(6):1702638.

90. Kuba K, Imai Y, Penninger JM. Angiotensin-converting enzyme 2 in lung diseases. *Curr Opin Pharmacol.* 2006;6(3):271-276.

91. Farha S, Heresi GA. COVID-19 and Pulmonary Arterial Hypertension: Early Data and Many Questions. *Ann Am Thorac Soc.* 2020;17(12):1528-1530.

92. Sahay S, Farber HW. Management of hospitalized patients with pulmonary arterial hypertension and COVID-19 infection. *Pulm Circ.* 2020;10(3):2045894020933480.