Increased Odds of Death for Patients with Interstitial Lung Disease and COVID-19: A Case–Control Study

To the Editor:

Coronavirus disease (COVID-19) is an international public health emergency. Although the prevalence of chronic respiratory disease in patients with COVID-19 has been reportedly low (1.5%), it is associated with increased risk of severe disease and—in chronic obstructive pulmonary disease—increased mortality (1–3). Together with numerous previously reported risk factors for severe COVID-19 (1–6), it has been hypothesized that patients with interstitial lung diseases (ILDs) may have poorer outcomes from COVID-19 (7). In this letter, we present the results of a multicenter retrospective case–control study examining outcomes from COVID-19 in patients with preexisting ILD.

Methods

Adult patients (greater than 18 yr old) with preexisting ILD who had COVID-19 diagnosed by real-time PCR or with negative real-time PCR but positive IgM and/or IgG serology between March 1 and June 8, 2020, at six Mass General Brigham hospitals were identified using the electronic health record–integrated centralized clinical data registry. ILD was defined as physician diagnosis or, if no pulmonology visit existed in our system, as radiologic evidence with confirmatory histopathology. Patients with lung transplantation were excluded. A control cohort with COVID-19 but without ILD was identified from the same registry and preliminarily matched by age ± 5 years, sex, white/nonwhite race, and comparative health using an automated method. Control subjects were confirmed not to have ILD through medical record review, and 2:1 matching was manually verified. Other than ILD, no other comorbidities were restricted from the control cohort. Data on demographics, medical history, medications, and outcomes were collected on both cohorts; pulmonary function, computed tomographic ILD pattern, and laboratory and therapeutic data were collected on the ILD cohort. The definition of the usual interstitial pneumonitis (UIP) pattern was inclusive of both definite and probable radiographic criteria. The primary outcome of interest was death, censored on June 8, 2020. Secondary outcomes included hospital admission, ICU admission, and hospital discharge either to the home or a skilled nursing facility. Statistical analyses were performed with Wilcoxon rank-sum test, Fisher exact test, and simple and multiple logistic regression adjusting for variables of statistical and clinical interest using R 3.6.1 (https://www.r-project.org). The study was deemed exempt from informed consent by the Mass General Brigham Institutional Review Board (protocol 2020P001397).

Results

We identified 306 patients with ILD who underwent testing for COVID-19, of whom 46 (15%) were positive and included in our study. Of 3,091 COVID-19–positive patients without ILD, we selected 92 (3%) control subjects matched for age, sex, and race. Of note, only one case had negative real-time PCR with positive serologies for both IgM and IgG. All control subjects had positive real-time PCR results. Fifteen (33%) of the 46 COVID-19–positive patients with ILD died compared with 12 (13%) of the 92 control subjects without ILD, representing an increased odds ratio of death in patients with ILD of 3.2 (95% confidence interval, 1.3–7.3; $P = 0.01$) (Table 1). Increased mortality was observed even after adjustment for age, sex, race, smoking status, cardiovascular disease (congestive heart failure and/or coronary artery disease), and any chronic immunosuppression (odds ratio, 4.3; 95% confidence interval, 1.4–14.0; $P = 0.01$). Additional analyses including chronic oxygen supplementation, chronic corticosteroid use alone, or other chronic immunosuppression did not affect the significance of the association between ILD and odds of death. Of note, two cases remained hospitalized at the time of censorship, one of whom was on mechanical ventilation. Compared with patients without ILD, COVID-19–positive patients with ILD were more likely to be admitted to the hospital and to require ICU care. Furthermore, they were less likely to be discharged from the hospital, particularly to the home.

Comparing survivors and nonsurvivors in the ILD cohort, nonsurvivors were significantly older (Table 2). We did not find evidence of an association between death from COVID-19 and male sex, race, obesity, smoking status, hypertension, diabetes, cardiovascular disease, or obstructive lung disease. The UIP pattern, present in 11 (24%) of all patients with ILD, was more common in nonsurvivors (40% vs. 16%; $P = 0.14$), although this was not significantly associated with death in this small subset of cases. Of those with UIP, antifibrotics were exclusively used by survivors. Overall, investigational therapies were not associated with death, although there was a trend toward more frequent treatment with hydroxychloroquine in nonsurvivors.

Discussion

In this case–control study, patients with ILD who contracted COVID-19 had a greater than fourfold increased adjusted odds of death, were more likely to be hospitalized and require ICU level of care, and were less likely to be discharged, particularly to the home, compared with a matched cohort of patients with COVID-19 without ILD. Accordingly, this study suggests that comorbid ILD is a risk factor for poor outcomes from COVID-19.

We observed increased odds of worse outcomes in patients with COVID-19 with underlying ILD. One explanation could be their limited pulmonary reserve. Suitably, nonsurvivors with ILD had a lower diffusion capacity and higher frequency of fibrotic UIP, although this was not statistically different from survivors. In

A.J.E. was supported by a fellowship grant from the NIH/NHLBI (F32 HL151132). A.J.G. was supported by a training grant from NIH/NHLBI (T32 HL007427). R.K.P. was supported by an NIH/NHLBI grant (K08 HL140087). L.E.F. was supported by an NIH/NHLBI grant (R01 HL137366). S.Y.E.-C. was supported by an NIH/NHLBI grant (R01 HL130275). R.M.B. was supported by NIH/NHLBI grants (R01 HL142093 and R21 HL145246). G.M.H. was supported by NIH/NHLBI grants (R01 HL111024, R01 HL130974, and R01 HL135142). T.J.D. was supported by an NIH/NHLBI grant (R03 HL148484).

This letter has a related editorial.

Originally Published in Press as DOI: 10.1164/rccm.202006-2441LE on September 8, 2020

Table 1. Clinical Characteristics of Patients with COVID-19 and Comorbid ILD Compared with a Matched Cohort of Patients with COVID-19 without Comorbid ILD

	ILD (*n* = 46)	No ILD (*n* = 92)	Odds Ratio (95% CI)	*P* Value
Patient characteristics				
Age, yr, median (IQR)	69 (58–78)	69 (59–78)	NA	NS
Sex, M, *n* (%)	16 (35)	32 (35)	NA	NS
Race, *n* (%)				NS
White	19 (41)	38 (41)	NA	
Black	9 (20)	27 (29)	NA	
Hispanic	12 (26)	13 (14)	NA	
Other	6 (13)	14 (15)	NA	
BMI, kg/m^2, median (IQR)	27.6 (22.5–33.2)	28.7 (23.7–33.5)	NA	NS
Smoking status, *n* (%)				0.07
Never-smoker	19 (41)	57 (62)	NA	
Current smoker	4 (9)	5 (5)	NA	
Former smoker	23 (50)	30 (33)	NA	
Pack-years, median (IQR)	32.5 (15.0–40.0)	15.0 (8.0–27.8)	NA	NS
Comorbidities, *n* (%)				
Diabetes mellitus	16 (35)	31 (34)	NA	NS
Hypertension	35 (76)	62 (67)	NA	NS
Cardiovascular disease	23 (50)	30 (33)	NA	0.06
Obstructive lung disease	15 (33)	25 (27)	NA	NS
Chronic therapies, *n* (%)				
Home oxygen supplementation	5 (11)	3 (3)	NA	NS
Inhaled corticosteroid	10 (22)	15 (16)	NA	NS
Long-acting β-agonist	7 (15)	6 (7)	NA	NS
Long-acting muscarinic antagonist	3 (7)	1 (1)	NA	NS
Corticosteroid	11 (24)	4 (4)	NA	0.001
Other immunosuppression*	18 (39)	7 (8)	NA	<0.001
ACEi/ARB	17 (37)	32 (35)	NA	NS
Nonsteroidal antiinflammatory	7 (15)	8 (9)	NA	NS
Outcomes, *n* (%)				
Hospital admission†	34 (74)	53 (58)	2.1 (0.9–4.6)	0.07
ICU level of care	16 (47)	12 (23)	3.0 (1.2–7.9)	0.02
Mechanical ventilation	13 (81)	11 (92)	0.4 (0.03–3.1)	NS
Length of stay, d	7 (5–13)	7 (5–14)	NA	NS
Discharged	17 (50)	45 (85)	0.2 (0.06–0.5)	<0.001
Home	9 (28)	31 (58)	0.3 (0.1–0.7)	0.008
Skilled nursing facility	8 (25)	14 (26)	0.9 (0.3–2.6)	NS
Death	15 (33)	12 (13)	3.2 (1.3–7.3)	0.01

Definition of abbreviations: ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; CI = confidence interval; COVID-19 = coronavirus disease; ILD = interstitial lung disease; IQR = interquartile range; NA = not applicable; NS = not significant ($P > 0.1$).
*Other immunosuppression in the ILD cohort includes mycophenolate mofetil ($n = 4$; 22%), rituximab ($n = 7$; 39%), tacrolimus ($n = 1$; 6%), and other ($n = 9$; 50%). All seven non-ILD cohort immunosuppression medications were other ($n = 7$; 8%).
†The percentages in subgroups were calculated using the parent group (i.e., the denominator for ICU level of care was hospital admission).

addition, COVID-19 could lead to an acute exacerbation of ILD. Though debated, some studies suggest that viral infections may associate with ILD exacerbations (8). Finally, although the RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial demonstrated that use of corticosteroids to treat COVID-19 was beneficial (9), use of chronic immunosuppression to treat underlying ILD has raised concerns that it may increase risk of disease (4). In our study, although patients with ILD had significantly increased use of chronic corticosteroids and other chronic immunosuppression compared with patients without ILD, the increased odds of death in the ILD cohort remained significantly elevated even after adjustment for chronic corticosteroid and/or other immunosuppression use. Similarly, frequency of chronic corticosteroid or other immunosuppression use, though higher in nonsurvivors compared with survivors, was not statistically associated with death. These results are consistent with those from previous coronavirus epidemics, notably severe acute respiratory syndrome and Middle East respiratory syndrome, in which chronic immunosuppression did not portend worse outcomes (10). Additional studies are needed to further assess safety of chronic immunosuppression in COVID-19.

Our study had the following limitations: *1*) As a case–control study, it is possible that there are additional confounding variables for which we did not account. *2*) Although our observations suggest that ILD may be an independent risk factor for worse outcomes from COVID-19, our small sample size limits comprehensive assessments of other risk factors for poor outcomes within the ILD cohort. *3*) Given the limited sensitivity of real-time PCR for COVID-19, it is possible that we missed additional cases who were negative by this initial testing modality. Despite this limitation, we had a high prevalence of COVID-19 in the ILD cohort (15%), although this may be due to confounding by testing

Table 2. Clinical Characteristics of Patients with ILD and COVID-19 Stratified by Death

	Survivors (*n* = *31; 67%*)	Nonsurvivors (*n* = *15; 33%*)	*P* Value
Patient characteristics			
Age, yr, median (IQR)	67 (55–72)	76 (65–90)	0.02
Sex, M, *n* (%)	11 (35)	5 (33)	NS
Race/ethnicity, *n* (%)			NS
White	11 (35)	8 (53)	
Black	6 (19)	3 (20)	
Hispanic	9 (29)	3 (20)	
Other	5 (16)	1 (7)	
BMI, kg/m^2, median (IQR)	27.9 (22.5–34.0)	24.0 (22.4–31.9)	NS
Smoking status, *n* (%)			NS
Never-smoker	12 (39)	7 (47)	
Former smoker	16 (52)	7 (47)	
Current smoker	3 (10)	1 (7)	
Pack-years, median (IQR)	35.0 (15.0–47.5)	32.5 (15.3–40.0)	NS
Comorbidities, *n* (%)			
Diabetes mellitus	11 (35)	5 (33)	NS
Hypertension	22 (71)	13 (87)	NS
Cardiovascular disease	15 (48)	8 (53)	NS
Obstructive lung disease	11 (35)	4 (27)	NS
Chronic therapies, *n* (%)			
Home oxygen supplementation	2 (10)	3 (20)	NS
Inhaled corticosteroid	9 (29)	1 (7)	NS
Long-acting β-agonist	6 (19)	1 (7)	NS
Long-acting muscarinic antagonist	1 (3)	2 (13)	NS
Corticosteroid	6 (19)	5 (33)	NS
Other immunosuppression*	11 (35)	7 (47)	NS
Antifibrotic	3 (10)	0 (0)	NS
ACEi/ARB	12 (39)	5 (33)	NS
Nonsteroidal antiinflammatory	4 (13)	3 (20)	NS
Pulmonary characteristics			
UIP (definite or probable),† *n* (%)	5 (16)	6 (40)	NS
FEV_1% predicted, median (IQR)	81 (67–90)	80 (63–104)	NS
FVC% predicted, median (IQR)	79 (67–94)	79 (61–99)	NS
FEV_1/FVC% predicted, median (IQR)	77 (73–85)	83 (79–87)	0.09
TLC% predicted, median (IQR)	80 (65–85)	73 (68–88)	NS
D_{LCO}_Hb% predicted, median (IQR)	58 (45–70)	37 (25–63)	NS
Admission laboratories			
D-dimer, ng/ml, median (IQR)	1,377 (919–1,996)	1,965 (892–4,000)	NS
C-reactive protein, mg/ml, median (IQR)	36.4 (24.8–103.8)	85.0 (56.4–146.5)	NS
Ferritin, ng/ml, median (IQR)	297 (206–506)	701 (314–2,483)	0.02
Troponin, ng/L, median (IQR)	18.0 (7.8–45)	37.0 (20–66)	0.06
Lactate, mmol/L, median (IQR)	1.4 (1.1–1.9)	1.9 (1.6–2.4)	>0.05
IL-6, pg/ml, median (IQR)	23.6 (5.8–216.6)	67.6 (28.5–212.0)	NS
Acute kidney injury, *n* (%)	6 (30)	7 (47)	NS
Liver function abnormalities, *n* (%)	7 (39)	8 (57)	NS
Therapies, *n* (%)			
Hydroxychloroquine	4 (13)	6 (40)	0.06
Remdesivir	5 (17)	1 (7)	NS
Tocilizumab	2 (7)	4 (27)	NS
Steroids (new or increased dose)	3 (10)	1 (7)	NS
Outcomes, *n* (%)			
Hospital admission‡	19 (61)	15 (100)	0.004
ICU level of care	6 (32)	9 (60)	NS
Mechanical ventilation	5 (83)	8 (89)	NS
Length of stay, d	7 (5–14)	6 (5–13)	NS
Venous thromboembolism	3 (9)	3 (20)	NS

Definition of abbreviations: ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; COVID-19 = coronavirus disease; D_{LCO}_Hb = D_{LCO} adjusted for Hb; ILD = interstitial lung disease; IQR = interquartile range; NS = not significant ($P > 0.1$); UIP = usual interstitial pneumonitis.

*Other immunosuppression in the survivor cohort includes mycophenolate mofetil (*n* = 2; 18%), rituximab (*n* = 5; 45%), tacrolimus (*n* = 1; 9%), and other (*n* = 5; 45%). In the nonsurvivor cohort, other immunosuppression includes mycophenolate mofetil (*n* = 2; 29%), rituximab (*n* = 2; 29%), and other (*n* = 4; 57%).

†UIP (definite or probable by computed tomography) included idiopathic pulmonary fibrosis (*n* = 6), connective tissue disease–associated UIP (*n* = 4), and combined pulmonary fibrosis and emphysema (*n* = 1). Non-UIP diagnoses included non-UIP connective tissue disease–associated ILD (*n* = 10), cryptogenic organizing pneumonia (*n* = 5), nonspecific interstitial pneumonitis (*n* = 3), hypersensitivity pneumonitis (*n* = 3), non-UIP combined pulmonary fibrosis and emphysema (*n* = 2), smoking-associated ILD (*n* = 2), sarcoidosis (*n* = 1), lymphangioleiomyomatosis (*n* = 1), pleuroparenchymal fibroelastosis (*n* = 1), and unclassifiable (*n* = 7).

‡The percentages in subgroups were calculated using the parent group (i.e., the denominator for ICU level of care was hospital admission).

rather than an increased susceptibility given the overlap between ILD and COVID-19 symptoms. This confounding, however, would tend to bias our data toward the null by capturing patients with less severe disease. *4*) Constrained geographic area potentially limits the generalizability of our conclusions. Ongoing larger international studies will help further elucidate the risk factors and outcomes of patients with ILD and COVID-19.

In summary, in this multicenter case–control study, patients with ILD, particularly those of advanced age, had increased odds of severe disease and death from COVID-19. Patients with ILD should be counseled of their increased risk, with an emphasis on public health measures to prevent infection in this susceptible population. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Effect of Positive End-Expiratory Pressure and Proning on Ventilation and Perfusion in COVID-19 Acute Respiratory Distress Syndrome

To the Editor:

Assessment of lung ventilation and perfusion of coronavirus disease (COVID-19) with acute respiratory distress syndrome (C-ARDS) is still scarce, especially in response to positive end-expiratory pressure (PEEP) and prone positioning. The objective of this study was to describe the physiological effects of PEEP and prone position on respiratory mechanics, ventilation, and pulmonary perfusion in patients with C-ARDS.

Methods

ARDS was defined according to the Berlin definition (1), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was confirmed by positive nasopharyngeal PCR. Patients were included consecutively, within 72 hours of intubation, if the electrical impedance tomography (EIT) device was available. Patients with a contraindication to esophageal catheter (esophageal stenosis, varices, or ulceration in particular) and/or impedancemetry (pacemaker, implantable defibrillator, or skin lesion) were excluded. Patients were deeply sedated and paralyzed. An EIT (Enlight 1800; Timpel) assessed regional ventilation and perfusion. Lung perfusion was recorded during an expiratory pause by injecting a 10-ml bolus of 7.5% hypertonic saline solution into a central venous catheter. Respiratory mechanics, ventilation, and perfusion EIT data were recorded at three arbitrary levels of PEEP (18, 12, and 6 cm H_2O) in the supine position and at PEEP 12 cm H_2O after 3 (2–4) hours of prone position. Arterial blood gases were collected prior

Author Contributions: F.P. and S.T.: study design; data collection, analysis, and interpretation; and script writing. T.M.: data collection, analysis, and interpretation. G.A.: data analysis and interpretation. M.V.: data analysis. A.-F.H.: data collection. N.D.P.: data interpretation. M.A.: data analysis and interpretation. G.C.: study design and data analysis and interpretation. A.M.D.: study design, data analysis and interpretation, and script writing. All authors: revision of the drafted manuscript and approval of its final version.

Originally Published in Press as DOI: 10.1164/rccm.202008-3058LE on October 19, 2020