Mortality Risk from COVID-19 among Unvaccinated Subjects with Autoimmune Phenotypes of Interstitial Lung Disease

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Research Article

Keywords: Mortality Risk, COVID-19, Unvaccinated Subjects, Autoimmune Phenotypes, Interstitial Lung Disease

Posted Date: October 22nd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-913501/v1

Abstract

Background: The impact of the SARS-CoV-2 virus on patients with interstitial lung disease (ILD) remains poorly understood. As patients with ILD often have severe underlying lung parenchymal involvement, and immunosuppressive therapy is common in this population, they are presumed to be at high risk for severe COVID-19 pneumonitis. We investigated differences between those with ILD who tested positive for the SARS-CoV-2 virus compared to those with ILD who did not, and explored the relationship with use of immunosuppressive therapy.

Methods: In this retrospective cohort study, we identified patients evaluated at the University of Chicago in 2020 with a multidisciplinary diagnosis of ILD, and stratified by detection of the SARS-CoV-2 virus presence or absence on PCR. Demographic data, laboratory values, and pulmonary function testing values were obtained at time of ILD diagnosis. Immunosuppressive therapies received since ILD diagnosis were assessed, as was mortality. Variable comparisons were determined by two-sided t-tests, or chi-square tests as appropriate, and logistic regression models were fitted to assess the odds of death from COVID-19 using generalized linear models with maximum-likelihood estimation.

Results: Of the 309 individuals with ILD in our cohort, 6.8% (n=21) tested positive for SARS-CoV-2. Those that were SARS-CoV-2 positive were younger (57 yrs vs 66 yrs; *P*=0.002), had baseline higher TLC (81% vs 73%, *P*=0.045), similar FVC (71% vs. 67%, *P*=0.37), and similar DLCO (71% vs. 62%, *P*=0.10) at baseline. Among patients with ILD and COVID-19, 67% had received immunosuppressive therapies compared to 74% of those with ILD without COVID-19. Those with ILD and COVID-19 were also more likely to have had a diagnosis of autoimmune related-ILD (CTD-ILD or IPAF) (62% vs 38%, *P*=0.029), and were more frequently hypoxemic ($SpO_2 \leq 92\%$; 4% vs 19%; *P*=0.012) at ILD diagnosis than those without COVID-19. The majority of patients (62%) with COVID-19 had received lymphocyte-depleting immunosuppressive therapy prior to infection. Overall, the mortality hazard was highest amongst unvaccinated subjects with autoimmune related-ILD who had COVID-19 (OR=9.6, 95%CI=1.7-54.0; *P*=0.01).

Conclusion:

SARS-CoV-2 is prevalent in ILD, and may put those who are younger, with autoimmune ILD, and on immunosuppressive therapy at higher risk. Larger studies are needed to fully explore the relationship between ILD and immunosuppressive therapy in COVID-19.

Background

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome (SARS) associated coronavirus 2 (SARS-CoV-2) and it remains an emergent threat to public health. The widespread systemic effect exerted by COVID19 suggests an exuberant immune response. This is supported by recent investigations that demonstrate a causal relationship between immune dysregulation and release of pro-inflammatory cytokines from SARS-CoV-2 infection.[1-3] Involvement of

these pathogenic pathways has refocused the spotlight on immunomodulatory therapies for COVID-19, and the importance of vaccination to reduce mortality.[4,5]

The interstitial lung diseases (ILD) comprise a heterogeneous group of disorders.[6,7] A significant proportion of patients who have ILD will have an autoimmune-related form of the disease. These specific diagnoses include those associated with defined connective tissue disease (CTD-ILD), and those who show clinical or serologic features consistent with connective tissue disease (CTD) without meeting established CTD diagnostic criteria, currently referred to as interstitial pneumonia with autoimmune features (IPAF)[7]. Many of these individuals receive immunosuppressive therapy. While these therapies are of great overall benefit, the higher propensity for systemic infections often puts patients at increased risk for acute ILD exacerbations and mortality.[8]

Notably, infection with respiratory viruses such as SARS-CoV-2 increases mortality risk in ILD. However, vaccination against respiratory viruses in patients with ILD effectively boosts production of protective IgG antibodies.[8] Whether SARS-CoV-2 infection heightens the risk for mortality/poor outcomes in unvaccinated patients receiving immunosuppressive therapies for autoimmune-related ILD is unclear. Here, we performed a single-center retrospective study for the year 2020, prior to the widespread distribution of vaccines. We hypothesized that SARS-CoV-2 infection in unvaccinated patients receiving immunosuppressive therapy for autoimmune-related ILD would increase the risk of detrimental outcomes.

Methods

In this retrospective cohort study, we identified patients with a multidisciplinary diagnosis of ILD evaluated at the University of Chicago between January 1, 2020 to December 31, 2020, who were enrolled in the Natural History of ILD registry (IRB#14163A), and stratified by detection of the SARS-CoV-2 virus presence or absence on PCR. Demographic data and pulmonary function testing values were obtained at time of ILD diagnosis. Immunosuppressive therapies received since ILD diagnosis were assessed. Corticosteroid therapy was noted if ≥20 mg of prednisone or its equivalent was given for at least three months. Vital status was determined from chart review and social security death index.

Statistical analysis

We conducted hypothesis testing using SARS-CoV-2 virus presence or absence on PCR as a binary variable to determine prevalence across predefined features of the ILD cohort. Variable comparisons were determined by two-sided *t* tests, Mann–Whitney *U* tests, or chi-square tests as appropriate. To examine the association of SARS-CoV-2 and all-cause mortality in patients with ILD, presence of autoimmune-related ILD was treated as a binary variable, and duration of follow-up was treated as a continuous variable. We calculated survival time as time from baseline ILD evaluation to death, lung transplantation, loss to follow-up, or end of study period. Survival time was censored on April 30, 2021 or if lost to follow-

up. Logistic regression models were fitted for assessment of the mortality outcome using generalized linear models with maximum-likelihood estimation. (2019.R.16; StataCorp).

Results

Of the 309 individuals with ILD in our cohort, 6.8% (n=21) tested positive for SARS-CoV-2. Those that were SARS-CoV-2 positive were younger (57 yrs vs 66 yrs; *P*=0.002), had baseline higher TLC (81% vs 73%, *P*=0.045), similar FVC (71% vs. 67%, *P*=0.37), and similar DLCO (71% vs. 62%, *P*=0.10) at baseline, similar prevalence of honeycomb fibrosis (43% vs 30%; *P*=0.22), similar baseline leukocyte count (9.4 vs 8.4; *P*=0.27) and marginally lower CRP (4.9 vs 9.3; *P*=0.07) (Table 1).

Table 1

Demographic characteristics of interstitial lung disease (ILD) cohort.

Characteristics of ILD cohort (n=309)	COVID-19 Positive (n=21)	COVID-19 Negative (n=288)	*P*-value
Age, mean (±SD)	57.3 (16)	66.0 (12)	**0.002**
Male gender, n (%)	7 (33)	111 (39)	0.64
Race			
Caucasian, n (%)	11 (52)	131 (58)	0.59
BMI, mean (±SD)	30.2 (5)	31.0 (7)	0.61
Ever smoker, n (%)	8 (38)	127 (44)	0.59
Smoking, pk-yrs, mean (±SD)	5 (9)	10 (18)	0.21
Gastroesophageal reflux, n (%)	14 (67)	173 (60)	0.55
Emphysema, n (%)	4 (19)	81 (28)	0.36
CAD, n (%)	3 (14)	48 (17)	0.78
DM, n (%)	5 (24)	63 (22)	0.89
Hypothyroidism, n (%)	5 (24)	46 (16)	0.35
TLC (% predicted) (±SD)	80.1 (16)	73.0 (17)	**0.045**
FVC (% predicted) (±SD)	71.2 (17)	67.4 (18)	0.37
FEV1 (% predicted) (±SD)	71.2 (19)	76.7 (16)	0.21
DLCO (% predicted) (±SD)	70.9 (18)	61.6 (23)	0.10
Radiologic honeycombing, n (%)	9 (43)	86 (30)	0.22
CTD-ILD/IPAF, n (%)	13 (62)	109 (38)	**0.029**
Corticosteroid therapy, n (%)	13 (62)	150 (52)	0.38
ANA seropositivity, n (%)	8 (42)	134 (49)	0.56
CRP titer, mean (±SD)	4.9 (2.2)	9.2 (9.6)	0.07
WBC, mean (±SD)	9.4 (9)	8.4 (3)	0.27
Lymphocyte %, mean (±SD)	28 (17)	21 (10)	**0.029**

Died, n (%)	3 (14)	11 (4)	**0.026**

Data are n (%) or mean ± standard deviation; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Exception for participants: ANA (antinuclear antibody) seropositivity ≥1:320, n=292; BMI (body mass index), n=223; Ever smoker, n=302; Emphysema, n=307; honeycombing, n=122; WBC (white blood cell count), n=89; TLC (total lung capacity), n=299; FVC (forced vital capacity), n=302; FEV1 (forced expiratory volume in 1st second), n=303; DLCO (diffusing capacity of the lungs for carbon monoxide), n=279; and other ILD, n=95. CAD=coronary artery disease; DM=diabetes mellitus; CRP=c-reactive protein; CTD=connective tissue disease; ILD=interstitial lung disease; IPAF=interstitial pneumonia with autoimmune features.

Among patients with ILD and COVID-19, 67% had received immunosuppressive therapies compared to 74% of those with ILD without COVID-19. Those with ILD and COVID-19 were also more likely to have had a diagnosis of autoimmune related-ILD (CTD-ILD or IPAF) (62% vs 38%, *P*=0.029), higher baseline lymphocyte counts (28% vs 21%, *P*=0.025), and were more frequently hypoxemic ($SpO_2 \leq 92\%$; 4% vs 19%; *P*=0.012) at ILD diagnosis than those without COVID-19. The majority of patients (62%) with COVID-19 had received lymphocyte-depleting immunosuppressive therapy (prednisone, azathioprine, mycophenolate, rituximab) prior to infection. At time of SARS-CoV-2 detection, CRP titers were much higher (52 mg/L vs 5mg/L; *P*=0.006) than at ILD diagnosis, however, the lymphocyte fraction was not different (24% vs 28%; *P*=0.52) (Fig. 1A). Not surprisingly, unvaccinated ILD subjects with COVID-19 had higher odds of death than those without COVID-19 (OR=4.2, 95%CI=1.1-16.4; *P*=0.039). Interestingly, the mortality hazard was highest amongst unvaccinated subjects with autoimmune related-ILD who had COVID-19 (OR=9.6, 95%CI=1.7-54.0; *P*=0.01) (Fig. 1B-D).

Discussion

Our study examines the association of SARS-CoV-2 positivity in unvaccinated patients with underlying interstitial lung disease. Overall, 6.8% of our unvaccinated ILD population tested positive for SARS-CoV-2 in 2020, which is comparable to state-wide prevalence rates in Illinois in 2020 of about 7.5% (963,389 cases with a population around 12.8 million).[9]

We found that unvaccinated patients with ILD who tested positive for COVID-19 were younger and were more likely to have an autoimmune related-ILD (CTD-ILD or IPAF). We also found that subjects with COVID-19 and ILD had higher odds of death compared to those without, with the highest prevalence of mortality amongst those with auto-immune ILD. Interestingly, these findings reverse the favorable prognostic patterns commonly seen with auto-immune ILDs compared to other types of ILD.[10]Over half (62%) of our patients who tested positive for SARS-CoV-2 had received lymphocyte-depleting immunosuppressive therapy. However, immunosuppressive therapy was numerically higher in the ILD without COVID group compared to the COVID with ILD (74% vs 67%) though not statistically significant. Overall our data suggests that the risk for these patients may not be only attributable to being on immunosuppressive therapy, but that the underlying chronic autoimmune lung disease may accentuate their risk.

Additionally, those with COVID-19 and ILD were more frequently hypoxemic. Although the prevalence of honeycomb fibrosis was numerically higher, this was not statistically significant. This suggests that patients with ILD who are at the highest risk of COVID-19 may have a more aggressive autoimmune phenotype morphologically characterized by honeycombing fibrosis, and more profound hypoxemia. This study lends credence to the idea that immunosuppressed patients with ILD are a population in which vaccinations and non-pharmaceutical interventions should be prioritized for the prevention of COVID-19, as unvaccinated immunosuppressed patients with ILD and COVID-19 are at greater risk of death.[5]

Abbreviations

CI = Confidence Interval; CTD = connective tissue disease; DLCO = diffusion capacity of the lung for carbon monoxide; FVC = forced vital capacity; HR = hazard ratio; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; IPAF = interstitial pneumonia with autoimmune features; IRB = institutional review board; PFT = pulmonary function testing; SD = standard deviation

Declarations

Funding:

NIH K23HL146942

Conflict of Interest Disclosures:

RS, MP, AT, IBV, CTL, NG, RG, RJ, and JHC have nothing to disclose. AA has received speaking and advisory board fees from Boehringer Ingelheim and grant funding by the NIH. RV has received a grant from Genentech to study the genomics of autoimmune interstitial lung diseases. MES has received institutional funding for interstitial lung disease research from Boehringer-Ingelheim, and Galapagos, fees for clinical trial adjudication committee service from Fibrogen and editorial support from Boehringer Ingelheim

This study was approved by our local ethics and IRB committee #14163A

Consent for publication given

Availability of Data and Materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request. Additionally, most of the data generated or analysed during this study are included in this published article

Author's contributions:

Conception and design: RS, MP, and AA

Acquisition of data for the work: RS, MP, AT, IBV, CTL, NG, RB, RJ, RV, JHC, MES, and AA

Analysis and interpretation: RS, MP, and AA

Drafting the manuscript for important intellectual content: RS, MP, AT, IBV, CTL, NG, RB, RJ, RV, JHC, MES, and AA

Critical revision for important intellectual content: RS, MP, AT, IBV, CTL, NG, RB, RJ, RV, JHC, MES, & AA.

Final approval of the submitted manuscript and accountability for all aspects of the work: All authors (RS, MP, AT, IBV, CTL, NG, RB, RJ, RV, JHC, MES, AA).

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Figures

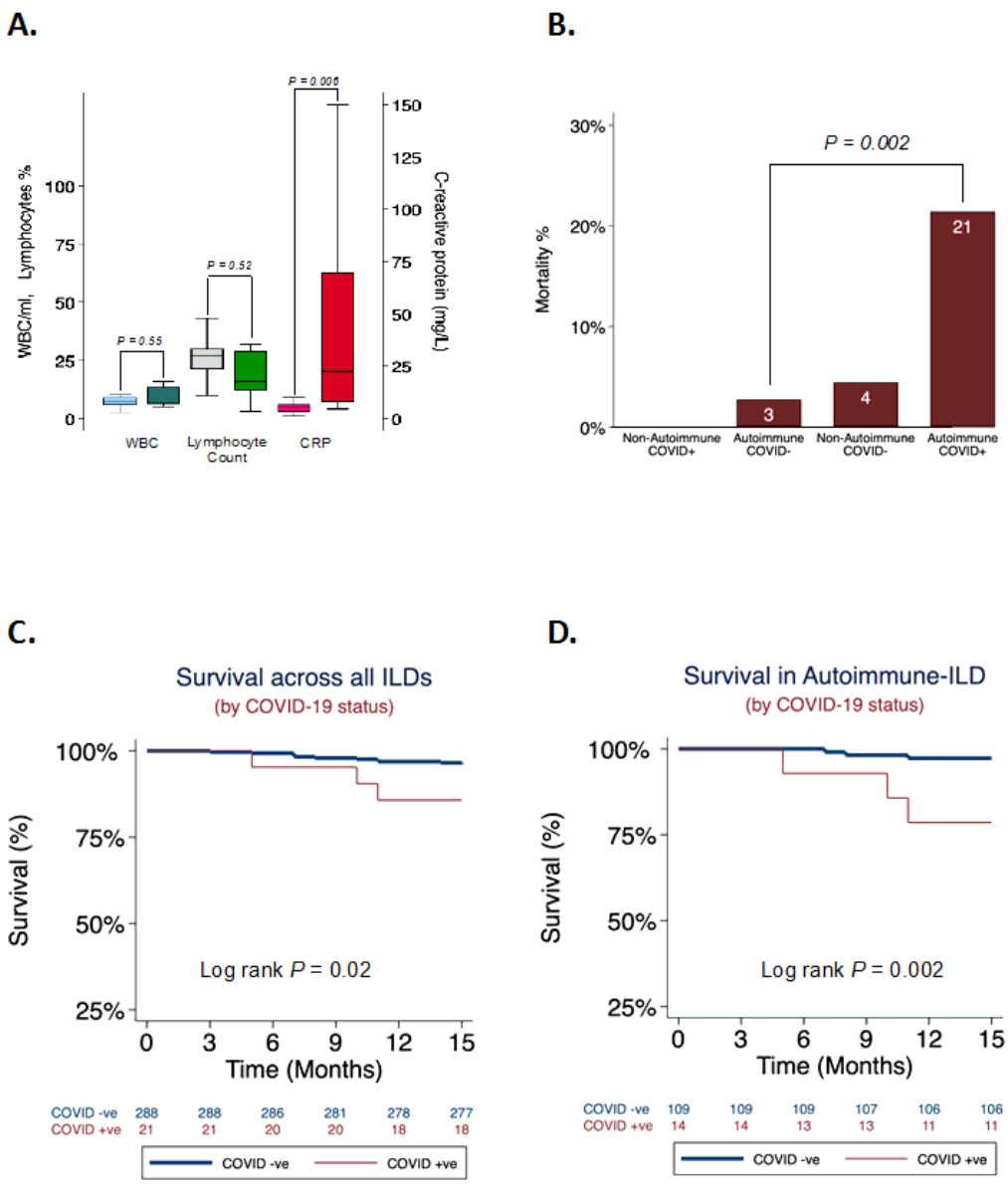

Figure 1

(A) Change in white blood cell (WBC) count, peripheral lymphocyte fraction (%) and c-reactive protein (CRP) titers before and after diagnosis of COVID19 in subjects with interstitial lung disease; (B) Mortality is highest among COVID-positive subjects with autoimmune-related interstitial lung disease (ILD); (C) Survival pattern by COVID19 status across all interstitial lung diseases (ILD); (D) Survival pattern by COVID19 status across autoimmune-related ILDs.