Mortality among Patients with COVID-19 and Different Interstitial Lung Disease Subtypes: A Multicenter Cohort Study.

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Conclusions
Our findings support that transcatheter embolotherapy should be considered, when possible, even for PAVMs with feeding artery sizes <3 mm (but not to the exclusion of other factors, like procedural risks and recurrent radiation exposure). Future research and HHT guideline iterations may need to direct their attention beyond PAVM feeding artery size as a risk factor for neurovascular complications and as a criterion for transcatheter embolotherapy application.

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Table 1. Mortality risk comparison between study and control cohorts

| Cohort                      | Patients in Cohort (after Matching) | Deceased Patients | Risk (%) | Risk Difference (%) | Confidence Interval (%) | P Value |
|-----------------------------|-------------------------------------|-------------------|----------|---------------------|-------------------------|---------|
| Patient with SARS-CoV-2 without IPF | 74,783                              | 2,648             | 3.5      | -2.0                | (-2.2 to -1.7)          | <0.0001 |
| Patient with SARS-CoV-2 with IPF    | 74,783                              | 4,113             | 5.5      | -2.9                | (-4.4 to -1.4)          | 0.0002  |
| Patient with SARS-CoV-2 without RA-ILD | 1,306                               | 35                | 2.7      | -1.3                | (-1.9 to -0.7)          | <0.0001 |
| Patient with SARS-CoV-2 with RA-ILD  | 1,306                               | 73                | 5.6      |                     |                         |         |
| Patient with SARS-CoV-2 without SSc-ILD | 5,639                               | 111               | 2.0      |                     |                         |         |
| Patient with SARS-CoV-2 with SSc-ILD  | 5,639                               | 183               | 3.2      |                     |                         |         |
| Patient with SARS-CoV-2 without Sjogren’s-ILD | 47,327                              | 816               | 1.7      | 0.2                 | (0.04 to 0.4)           | 0.02    |
| Patient with SARS-CoV-2 with Sjogren’s-ILD | 47,327                              | 723               | 1.5      |                     |                         |         |
| Patient with SARS-CoV-2 without HP   | 4,471                               | 115               | 2.6      | -0.7                | (-1.4 to -0.04)         | 0.04    |
| Patient with SARS-CoV-2 with HP      | 4,471                               | 148               | 3.3      |                     |                         |         |

Definition of abbreviations: HP = hypersensitivity pneumonitis; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; RA = rheumatoid arthritis; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SSc = scleroderma.

Table 2. Mortality risk comparison between study cohorts

| Cohort                      | Patients in Cohort (after Matching) | Deceased Patients | Risk (%) | Risk Difference (%) | Confidence Interval (%) | P Value |
|-----------------------------|-------------------------------------|-------------------|----------|---------------------|-------------------------|---------|
| Patient with SARS-CoV-2 with IPF    | 36,057                              | 1,417             | 3.9      | 2.1                 | (1.8 to 2.3)            | <0.0001 |
| Patient with SARS-CoV-2 with Sjogren’s-ILD | 36,057                              | 671               | 1.9      |                     |                         |         |
| Patient with SARS-CoV-2 with IPF    | 5,639                               | 186               | 3.3      | 0.1                 | (-0.6 to 0.7)           | 0.16    |
| Patient with SARS-CoV-2 with SSc-ILD  | 5,639                               | 183               | 3.2      |                     |                         |         |
| Patient with SARS-CoV-2 with Sjogrens-ILD | 5,639                               | 90                | 1.6      | 1.6                 | (1.1 to 2.2)            | <0.0001 |

Definition of abbreviations: ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SSc = scleroderma.

heterogeneous group of disorders, and it remains to be determined whether all ILDs or just specific subtypes have higher SARS-CoV-2–related mortality.

Methods
To address this, we performed a large, retrospective cohort study to evaluate outcomes from SARS-CoV-2 infection among patients with different ILD subtypes. Analyses were performed using data from the TriNetX Analytics Network, a global research network containing records from millions of patients (8–11). This large, multicenter database includes relevant information on diagnoses, procedures, medications, and laboratory values and incorporates patients from both the inpatient and outpatient environments. Patients included in our study were adults ≥18 years of age diagnosed with SARS-CoV-2 between the periods of January 1, 2020 to February 1, 2022. Patients with SARS-CoV-2 were identified based on diagnostic coding for coronavirus disease (COVID-19) or documentation of a positive polymerase chain reaction test result. Study cohorts included patients with one of the following ILD diagnostic subtypes: idiopathic pulmonary fibrosis (IPF), rheumatoid arthritis–ILD, scleroderma (SSc)-ILD, Sjogren’s syndrome with lung involvement, and hypersensitivity pneumonitis. Control cohorts had SARS-CoV-2 but no diagnosis of ILD. Study and control cohorts underwent propensity score matching for age, sex, history of nicotine dependence, body mass index, diabetes mellitus, ischemic heart disease, hypertensive disease, and cerebrovascular disease before analyses. Cohorts were not matched for other types of lung diseases. For mortality comparisons, we used “Deceased at 90 days” after SARS-CoV-2 diagnosis as our primary endpoint, and relative risk comparisons were performed on ILDs with more than 5,000 patients.

Results
We identified a total of 133,526 patients with SARS-CoV-2 and a diagnosis of ILD. Overall prevalence varied among different ILD subtypes, with IPF being the most prevalent (74,783 cases), followed by Sjogren’s with lung involvement (47,327) and SSc-ILD (5,639) (Table 1). After propensity score matching, the risk of mortality was increased for all ILD subtypes (IPF, rheumatoid arthritis–ILD, SSc-ILD, and hypersensitivity pneumonitis), with the exception of ILD from Sjogren’s syndrome, which had a lower overall mortality than matched control subjects (Table 1). For highly prevalent ILDs, a trend toward higher mortality risk was seen in IPF and SSc-ILD, as mortality risk for IPF and SSc-ILD were both higher than ILD in Sjogren’s syndrome (Table 2).

Discussion
ILD is recognized as a risk factor for death from SARS-CoV-2, but this study is the first to look at outcomes among patients with different ILD subtypes. Our major finding is that all ILDs increase mortality from SARS-CoV-2, with the exception of Sjogren’s syndrome, which had a lower mortality than control subjects.

Specific factors contributing to higher mortality among different ILD subtypes were not identified in our study. However, it is reasonable to assume that infection may have increased mortality by
accelerating progression or causing acute exacerbations, a manifestation of ILD known to associate with substantial morbidity and mortality. It is also possible that properties intrinsic to the ILD lung contributed to worsening outcomes; this includes the potential impact of dense regions of lung fibrosis on immune cell trafficking and the role of dysfunctional alveolar type 2 cells (12) and activated myofibroblasts on lung injury and repair (13, 14).

A surprising finding in our study was that patients with Sjogren’s syndrome had a reduced SARS-CoV-2 mortality. Interestingly, histopathological features of this disease are unique to other ILDs, which includes the infiltration of lymphocytes around airways and cystic dilation of distal airspaces (15, 16). Whether these structural changes somehow contribute to altering SARS-CoV-2 biology is unknown; however, we speculate that the binding of virus to epithelium may be reduced by the cystic dilation of airspaces. It is also tempting to speculate that factors specific to Sjogren’s syndrome may have influenced the course of disease. For example, autoantibodies to Ro52 target a protein already linked to neutralizing viruses (17).

Our study did not detect a significant increase in mortality in IPF versus other ILDs. This was somewhat surprising, given that IPF is considered the most aggressive ILD (16). Indeed, less than half of all patients with IPF are alive at 5 years, whereas the majority of patients with SSc-ILD are alive over a similar time period (18). Our observation that mortality was similar among patients with IPF and SSc-ILD challenges traditional thinking about the unique vulnerability of patients with IPF.

Although our study has many strengths, we also recognize it has weaknesses. As with any study that relies on administrative data, we recognize our results may have been skewed by inaccuracies in diagnostic coding. Also, other confounding variables not included in our analyses may have affected the results. Moreover, the interpretation of findings is limited without details about disease severity, antiviral treatments, underlying immunosuppressive drugs, and primary cause of death. Finally, some cohorts had small numbers of patients, making it hard to generalize our results to larger populations.

In conclusion, our study suggests that mortality related to SARS-CoV-2 is increased in patients with different subtypes of ILD, highlighting the importance of prevention and early treatment in this diverse patient population.

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