Pulmonary fibrosis 4 months after COVID-19 is associated with severity of illness and blood leucocyte telomere length

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ABSTRACT

The risk factors for development of fibrotic-like radiographic abnormalities after severe COVID-19 are incompletely described and the extent to which CT findings correlate with symptoms and physical function after hospitalisation remains unclear. At 4 months after hospitalisation, fibrotic-like patterns were more common in those who underwent mechanical ventilation (72%) than in those who did not (20%). We demonstrate that severity of initial illness, duration of mechanical ventilation, lactate dehydrogenase on admission and leucocyte telomere length are independent risk factors for fibrotic-like radiographic abnormalities. These fibrotic-like changes correlate with lung function, cough and measures of frailty, but not with dyspnoea.

INTRODUCTION

Reports of hospitalised COVID-19 survivors show that there are persistent symptoms, radiographic abnormalities and physiological impairments months after the initial illness. Persistent chest imaging abnormalities and histopathological findings of lung fibrosis were also found in a majority of survivors of the SARS-CoV-1 2003 outbreak, suggesting that the SARS viruses may lead to a worse fibroproliferative response than other pneumonias. Cohort studies of COVID-19 survivors report that severity of the initial illness is associated with a greater risk of persistent CT abnormalities, especially for patients requiring supplemental oxygen or mechanical ventilation, but independent clinical, biomarker and genomic risk factors have not been identified. Also, the extent to which CT findings correlate with symptoms and physical function remains unclear. To address knowledge gaps, we conducted a prospective cohort study of survivors hospitalised with severe COVID-19, half of whom were mechanically ventilated, with 4-month follow-up. We sought to characterise associations of pulmonary radiographic and physiologic sequela of severe COVID-19, and to identify independent risk factors for the development of post-COVID fibrosis.

METHODS

Additional details are included in the supplemental materials.

We conducted a single-centre prospective cohort study of adults hospitalised between 1 March 2020 and 15 May 2020 who required supplemental oxygen. At 4 months after hospitalisation, participants underwent a non-contrast high-resolution chest CT (HRCT) scan, pulmonary function testing, measurement of 6-minute walk distance (6MWD), assessment of the frailty phenotype and a blood draw for isolation of genomic DNA. Radiographic patterns were categorised and quantitated using a severity scoring system developed by ARDSnet and used in acute respiratory distress syndrome (ARDS) survivors, and classified into two groups (non-fibrotic or fibrotic). Fibrotic-like patterns included those with reticulations, traction bronchiectasis or honeycombing. Telomere length of genomic DNA isolated from blood drawn at the 4-month follow-up visit was measured by a quantitative PCR assay.

We calculated Spearman’s rank correlation coefficients between continuous data. We created separate generalised additive logistic models (GAMs) to test adjusted associations between the risk of fibrotic-like patterns on CT scan and independent continuous variables identified in univariable analysis. Due to the moderate cohort size and rate of fibrotic-like radiographic abnormalities, we used generalised covariate balanced propensity scores to adjust for potential confounders. We estimated adjusted ORs using logistic regression models if there was no evidence of non-linearity.

RESULTS

We enrolled 76 patients meeting eligibility criteria (online supplemental figure S1); demographic and clinical features are shown in online supplemental table S1. All participants required supplemental oxygen during hospitalisation, and 32 (42%) required mechanical ventilation.

A median of 4.4 (IQR 4.0–4.8) months after hospitalisation, the most common radiographic abnormality was ground glass opacities (43%), followed by reticulations (39%) and traction bronchiectasis (28%) (figure 1, online supplemental table S2). Fibrotic-like patterns were more common in those who were mechanically ventilated compared with those who were not (72% vs 20%, p=0.001) (online supplemental tables S1 and S4). In unadjusted analyses, those with fibrotic-like patterns were significantly more likely to be male, have shorter telomeres, higher admission Sequential Organ Failure Assessment (SOFA) scores, higher lactate dehydrogenase (LDH) levels and have received steroids or anti-interleukin-6...
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Brief communication

Figure 1  High-resolution CT (HRCT) scans of the chest from COVID-19 survivors. (A) Representative CT chest scans demonstrating no abnormalities (left), non-fibrotic patterns (middle) and fibrotic-like patterns (right). The upper panels show a coronal section and the lower panels show an axial image at the level just below the carina. The scan with a non-fibrotic pattern had a ground glass opacities (GGO) score of 5.6 (84th percentile in the group). The CT scan with a fibrotic-like pattern had a reticulation score of 6.4 (98th percentile), a traction bronchiectasis score of 5.0 (95th percentile) and no honeycombing. (B) Chest HRCT scores for radiographic patterns observed in the study cohort. The middle line of the boxplot represents the median score; bottom and top lines represent the 25th and 75th percentile, respectively. Where no lines are seen, the 25th, 50th and 75th percentile scores were all 0. The extent of each pattern was graded using a scoring system developed by ARDSnet.7 The possible range of scores was 0–20 from all categories of abnormalities, except traction bronchiectasis, which had a possible range of 0–5.

|  | Non-Fibrotic Pattern | Fibrotic-like Pattern |
|---|---|---|
| GGO Score | 5.6 | 5.0 |
| Reticulation Score | 0.4 | 0.5 |

Participants had an array of functional deficits (online supplemental table S5). Overall, 40 (53%) had a reduced diffusion capacity, 78% had a decreased 6MWD, 18% remained >10% below baseline weight and 53% had weak grip strength.

Ground glass, reticulations and traction bronchiectasis scores correlated more strongly with reduction in diffusion capacity (ρ = 0.34, −0.64 and −0.49, respectively, all p < 0.01) than FVC (table 1). Ground glass correlated with the frailty phenotype score, while reticulation and traction bronchiectasis correlated

Table 1  Spearman correlation coefficients of radiographic and dyspnoea scores with pulmonary function, 6-minute walk distance, frailty and symptoms

| CT pattern | DLCO (% predicted) R2 r P value | FVC (% predicted) R2 r P value | 6MWD (m) R2 r P value |
|---|---|---|---|
| Ground glass opacities | 0.12 −0.34 0.003* | 0.06 −0.25 0.03* | 0 −0.02 0.92 |
| Reticulations | 0.41 −0.64 <0.001* | 0.04 −0.21 0.07 | 0 −0.02 0.8 |
| Traction bronchiectasis | 0.24 −0.49 <0.001* | 0.05 −0.23 0.04* | 0 −0.05 0.69 |

| CT pattern | FRC phenotype score R2 r P value | Cough scale UCSD SOBQ R2 r P value | UCSD SOBQ R2 r P value |
|---|---|---|---|
| Ground glass opacities | 0.21 0.46 <0.001* | 0 0.07 0.56 | 0.02 0.14 0.23 |
| Reticulations | 0.05 0.23 0.04* | 0.07 0.26 0.02* | 0 0.06 0.66 |
| Traction bronchiectasis | 0.03 0.16 0.17 | 0.06 0.25 0.03* | 0 0.07 0.57 |

| DLCO (% predicted) R2 r P value | FVC (% predicted) R2 r P value | 6MWD (m) R2 r P value |
|---|---|---|
| UCSD SOBQ | 0.02 −0.14 0.24 | 0.06 −0.25 0.04* | 0.06 −0.25 0.03* |

| Frailty phenotype score | Grip strength (kg) R2 | Gait speed (m/s) R2 |
|---|---|---|
| UCSD SOBQ | 0.22 0.47 <0.001* | 0.14 −0.37 0.001* | 0.05 −0.21 0.06 |

*Significant after controlling for false discovery using the Benjamini-Hochberg method at a false discovery rate of 0.10.

DLCO, diffusion capacity for carbon monoxide; 6MWD, 6-minute walk distance; UCSD SOBQ, University of California San Diego Shortness of Breath Questionnaire.
with cough. Dyspnoea correlated more strongly with markers of weakness and deconditioning, including increased frailty score and reduced grip strength, than radiographic abnormalities (table 1). Similarly, the 6MWD was associated with the dyspnoea score and not with radiographic abnormalities.

Fully adjusted GAMs showed that both admission SOFA score and percent-predicted telomere length were linearly associated with the predicted risk of fibrotic-like radiographic abnormalities (figure 2). Duration of mechanical ventilation varied linearly with the predicted risk of fibrotic-like patterns through 20 days and plateaued with more prolonged mechanical ventilation. LDH levels also plateaued at higher levels. In fully adjusted logistic regression models, every 1-point increase in SOFA score, 50-point increase in LDH and 1 ventilator-day was associated with 1.49 (95% CI 1.17 to 1.89) and 1.07 (95% CI 1.03 to 1.12) higher odds of fibrotic-like patterns on CT scan, respectively. Each 10% decrease in age-adjusted telomere length was associated with a 1.35 higher odds of fibrotic-like patterns (95% CI 1.06 to 1.72). Sensitivity analyses are shown in online supplemental figures S3 and S4.

**DISCUSSION**

Pulmonary fibrosis is a feared complication of respiratory infections. We found that among survivors of severe COVID-19, 20% of non-mechanically ventilated and 72% of mechanically ventilated individuals had fibrotic-like radiographic abnormalities 4 months after hospitalisation. The presence of these radiographic abnormalities correlates with decrements in lung function, cough and frailty. Greater initial severity of illness, longer duration of mechanical ventilation and shorter blood leucocyte telomere length are independent risk factors for the development of fibrotic-like abnormalities.

Fibrosis was measured in this study both subjectively, in a manner congruent with other population-based, ARDS, SARS-CoV-14 and COVID-19 studies, as well as objectively using texture analysis. We include reticulations as a manifestation of fibrotic-like patterns to facilitate comparison to prior post-infectious studies, and acknowledge that reticulations may either resolve or progress over time. The presence of the pulmonary function degradations associated with these radiographic findings at 4 months is concerning for potential long-term damage. In the absence of longer-term follow-up, it is unclear if these functional and radiographic abnormalities represent permanent lung scarring.

This is the first study to identify age-adjusted telomere length as an independent risk factor for post-COVID lung fibrosis. Short blood leucocyte telomere lengths have been shown to be a risk factor for the development of different subtypes of fibrotic interstitial lung disease, including idiopathic pulmonary fibrosis (IPF). Here, we also find that longer telomere lengths appear to be protective, thus, this genomic biomarker may measure the balance of profibrotic and antifibrotic susceptibilities.
Limitations of this study include its small size, the lack of replication cohort and the need to use a propensity score to adjust for covariates. It is possible that acute illness may affect telomere length or that some imaging abnormalities were pre-existing. Patients were hospitalised prior to US Food and Drug Administration (FDA)-approved therapies, yet half received steroids.

Still, this study reveals significant respiratory symptoms and morbidity associated with severe COVID-19. Dyspnoea, reported by many survivors, correlates more strongly with muscle strength and frailty measures than radiographic pattern scores, suggesting persistent extrapulmonary effects, including cardiovascular or neuromuscular dysfunction. Additional prospective studies are needed to characterise temporal changes of post-COVID-19 fibrotic abnormalities, and clinical trials are needed to investigate therapeutic options to promote its resolution.

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Contributors CM, MRB and CKG conceptualised the study, CM, MAC and MRB recruited patients and collected samples and clinical data. DZ performed experiments and analysed data. MS, BD and EAH analysed imaging studies. CM, DZ, YW, MRB and CKG performed statistical analysis. CM, MRB and CKG wrote the manuscript.

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SUPPLEMENTAL MATERIALS

Pulmonary Fibrosis after COVID-19 is Associated with Severity of Illness and Blood Leukocyte Telomere Length

Supplemental Methods.

Table S1. Demographic and clinical features of COVID-19 survivors.

Table S2. Prevalence of HRCT abnormalities.

Table S3. Demographics and Clinical Factors between those with and without fibrotic patterns.

Table S4. Clinical Features of COVID-19 Survivors who underwent mechanical ventilation.

Table S5. Prevalence of CT abnormalities, lung function and physical impairment, and respiratory symptoms.

Table S6. Associations between independent variables of interest and fibrotic-like patterns in multivariable logistic regression.

Table S7. Spearman correlations of SOFA score, ventilator days, and age-adjusted percent telomere length with regression model covariables before and after covariate-balancing propensity score.

Figure S1. Study flow diagram

Figure S2. Continuous association of percent Ground Glass Opacity (GGO) and Ground Glass Reticulation (GGR) via adaptive multiple features method lung texture analysis and any radiographic abnormality and fibrotic-like abnormalities.

Figure S3. Sensitivity analysis of the continuous association of fibrotic-like abnormalities with SOFA score, lactate dehydrogenase, days of mechanical ventilation, and age-adjusted leukocyte telomere length (LTL) percentile using generalized additive models with LOESS smother.

Figure S4. Sensitivity analysis of the continuous association of fibrotic abnormalities as defined by Fleishner Society position paper with SOFA score, lactate dehydrogenase, days of mechanical ventilation, and age-adjusted leukocyte telomere length (LTL) percentile using generalized additive models with LOESS smother.
Supplemental Methods.

Study Design

We conducted a single-center prospective cohort study of adults age 21 years and older hospitalized between March 1, 2020 and May 15, 2020 with a positive SARS-CoV-2 RT-PCR nasopharyngeal swab and who required supplemental oxygen. The Columbia University Irving Medical Center (CUIMC) Institutional Review Board study protocol number is AAAR1916. Participants signed a written informed consent.

Recruitment and Enrollment

We identified prospective patients by chart review to exclude those with pre-existing ILD or a history of lung transplantation. We enrolled prospective participants by calling consecutive subjects meeting eligibility criteria based on their admission date, with sampling weighted to include approximately 50% survivors who underwent mechanical ventilation. We sought to enroll 70-100 participants based upon the capacity of the research team to recruit and assess participants during the 4-month follow-up study period of July and August 2020. Participants ambulated independently prior to hospitalization, did not live in a skilled-care facility prior to hospitalization, required supplemental oxygen therapy during their hospital stay, and were discharged to acute rehabilitation, subacute rehabilitation, or home. All participants were living at home prior to enrollment.

Electronic Medical Record Measurements

We obtained clinical data from the New York Presbyterian-CUIMC clinical data warehouse, which contains electronic data for inpatient and outpatient visits. Patient data included demographics, diagnoses, procedures, medications, laboratory tests, vital signs and ventilator flowsheet data, and other clinical variables. Past medical history diagnoses were retrieved from the hospital admission notes and by using groups of ICD-10 diagnosis codes.
according to the Clinical Classifications Software by the Healthcare Cost and Utilization Project. We calculated the Sequential Organ Failure Assessment (SOFA) score during the first 24 hour of admission.

**Chest Computed Tomography**

Non-contrast high resolution chest CT scans (HRCT) were performed at maximal inspiration using either GE VCT 64 or GE Revolution CT750 HD instrument. Two chest radiologists (MS and BD) evaluated the scans for radiographic abnormalities associated with post-acute ARDS and COVID-19, including ground glass opacities, intra-parenchymal opacities, non-emphysematous cysts, centrilobular nodules, reticulations, honeycombing, and traction bronchiectasis. Those with $\geq 5\%$ involvement of reticulations or honeycombing, or the presence of traction bronchiectasis, were categorized as having fibrotic-like radiographic patterns. All others with $\geq 5\%$ involvement of a lung quadrant were categorized as having non-fibrotic patterns. The radiographic abnormalities were scored using a semi-quantitative scoring system used by the ARDSnet investigators. Radiographic abnormalities were assessed at 5 levels: the aortic arch, 1cm above the diaphragm, and three levels equally spaced between the aortic arch and diaphragm. Each level was divided into four lung quadrants, and scored within each quadrant as: 0=no involvement; 1= <5% involvement; 2= 5–25% involvement; 3=26–49% involvement; 4=50–75% involvement; and 5=greater than 75% involvement. The sum of the quadrant scores at each level was averaged across the five levels to determine the final score (range 0-20). For traction bronchiectasis, an airway abnormality that is difficult to quantify, each level was scored as either 0 or 1 for its absence or presence, respectively, for a maximum score of 5.

In addition to the radiologists’ subjective scoring of fibrotic-like patterns, the University of Iowa imaging lab (Iowa City, IA, USA) used the adaptive multiple features method (AMFM) to
quantify HRCT scans for various lung features, including: ground glass opacity, ground glass-reticular, honeycombing, emphysema, or normal lung.

Clinical Measurements

Pulmonary function tests were performed on one of two pulmonary function machines (NDD EasyOne Pro, Andover MA; Vyaire Medical VMAX Encore, Mettawa IL). Pulmonary function testing and six-minute walk distance (6MWD) were assessed according to established guidelines. Cough was assessed using a 100mm visual analogue scale. Dyspnea was assessed using the UCSD shortness of breath questionnaire.

Frailty Measurements

We measured the five Fried Frailty domains: gait-speed, grip-strength, weight loss, low activity, and exhaustion. We measured grip-strength, gait-speed, and exhaustion, and using the traditional Cardiovascular Health Study (CHS) methodology. Weight loss was calculated as the difference between their hospitalization admission weight and the measured weight during the follow up visit. We used the CHS cutoff of a decrease >10 lbs. to define the presence of weight loss. We assessed the physical activity domain on the basis of report of activities performed at four-moth follow-up using the Duke Activity Status Index (DASI) instead of the Minnesota Leisure Time Physical Activity Questionnaire, the original CHS measure of physical activity, as we have shown that the DASI improves the construct and predictive validity of frailty assessments in acute respiratory failure survivors. We used previously validated DASI score cutoffs for low activity in older acute respiratory failure survivors (men ≤12.5; women ≤10).

Each frailty domain is assigned 1 point if present and 0 points if absent based on the aforementioned cutoffs (range, 0-5). Consistent with CHS methodology, we defined the frailty phenotype as being frail in ≥3 of the five domains.
**Genetic and Genomic Measurements**

Since neither blood nor genomic DNA was available for all participants from the time of the acute illness, blood was collected from each participant at the 4 month follow-up visit. DNA was isolated from blood leukocytes using the Gentra Puregene Blood kit (Qiagen, Valencia CA). Leukocyte telomere length (LTL) was measured using a quantitative PCR assay and the RotoGene real-type PCR system (Qiagen)\(^2\). The LTL was expressed as a logarithm-transformed ratio of telomere to single-copy gene \([\ln(T/S)]\) and this value was compared to LTL from normal control subjects (\(n=201\) unrelated multiethnic individuals from Dallas, TX, ranging in age from 19 to 89 years) to estimate an age-adjusted LTL percentile.

**Missing Data**

The Glasgow Coma Score, a component of the SOFA score, was missing for nearly all non-ICU patients, and we thus imputed a score of 15 for these participants based on previous literature\(^2\). Inflammatory markers ESR, CRP, LDH, Ferritin and D-dimer, had 6-12% missingness. We used the MICE function in R(v3.5.1) to perform multiple imputation using predictive mean matching for missing values\(^2\). There were six participants that could not perform the 6-minute walk test because they were non-ambulatory and one whose baseline heart rate was too high to safely perform the test. For the six participants who were non-ambulatory, we imputed 0 and ran a complete case analysis excluding the last participant. Three participants were unable to produce acceptable or reproducible DLCO measure. Therefore, we ran a complete case analyses using only participants with complete PFT data.

**Statistical Analyses**

We examined unadjusted associations of clinical and biomarker characteristics with no abnormalities, non-fibrotic pattern or fibrotic-like pattern using analysis of variance (ANOVA),
Kruskal Wallis, or chi-squared tests. We calculated correlation coefficients between continuous data using Spearman's method. We examined adjusted associations of fibrotic-like patterns with the hypothesized and biologically plausible independent variables that were associated with fibrotic-like patterns in unadjusted analyses. We used generalized covariate balanced propensity scores (CBPS) to adjust for potential confounders as has been done in prior studies, to avoid model overparameterization. We generated propensity scores predicting each of the independent variables of interest (Table S6) using the CBPS function in R(v3.5.1). To do so, we calculated CBPS for each independent variable by regressing it on a set of potential confounders. For all the independent variables, we included a list of common confounders, including age, sex, race/ethnicity, days since infection, body mass index, pack-years of smoking, and treatment with steroids while hospitalized in the generation of the CBPS. In addition, each CBPS score was generated with the other three independent variables of interest. For example, the SOFA CBPS included the common confounders (age, sex, etc.) plus LDH, days of mechanical ventilation, and telomere length. Thus, each GAM has only two variables: (1) the independent variable of interest and (2) the CBPS score for that variable, with collectively controls for the aforementioned potential confounders.

In the GAMs, we did not assume linear associations between continuous independent variables and risk of fibrotic-like abnormalities on CT scan, and instead estimated associations by a nonparametric locally weighted smoothing spline (LOESS). For lab values like LDH, we removed outliers beyond 2 standard deviations for the analysis. For independent variables without statistically significant non-linear associations with fibrotic-like abnormalities in the GAMs, we estimated adjusted odds ratios using logistic regression models. Conventional residuals and quantile residuals showed no substantive bias, had a mean of zero, and demonstrated constant variance across the predicted values, predictors and propensity scores.

Since LTL may increase severity of illness, and since LTL may be affected by critical illness, we conducted sensitivity analyses: one estimating associations of LTL, admission
SOFA score, LDH, and duration of mechanical ventilation with fibrotic-like patterns without adjusting for the other three independent variables. The second sensitivity analysis was performed with a more conservative definition of fibrosis that comprised only traction bronchiectasis and honeycombing. Covariates were found to be balanced in all propensity scores (see Table S7). Plots Analysis were performed using Stata/IC v16 (StataCorp) and R, v3.5.1.
| DEMOGRAPHICS | Total | Normal CT chest | Non-Fibrotic pattern | Fibrotic-like pattern | p-value* |
|--------------|-------|----------------|---------------------|----------------------|----------|
| Age, mean (SD) | 54.0 (13.7) | 51.8 (13.7) | 60.6 (10.8) | 53.4 (14.2) | 0.14     |
| Male (%) | 45 (61%) | 16 (52%) | 4 (31%) | 25 (78%) | 0.007    |
| Hispanic ethnicity | 43 (57%) | 14 (45%) | 10 (77%) | 19 (59%) | 0.17     |
| Race | | | | |  |
| White | 30 (39%) | 13 (42%) | 4 (31%) | 13 (41%) | 0.17     |
| Black | 22 (30%) | 13 (42%) | 4 (31%) | 5 (16%) | 0.17     |
| Asian | 1 (1%) | 0 | 0 | 1 (4%) | 0.17     |
| Other | 23 (30%) | 5 (16%) | 5 (38%) | 13 (41%) | 0.17     |
| Body Mass Index (kg/m²), mean (SD) | 32.2 (6.9) | 34.2 (7.8) | 32.7 (4.6) | 30.1 (6.4) | 0.07     |

| GENOMIC FACTORS | | | | | |
| Leukocyte telomere length, percentile (IQR) | 52 (49-68) | 52 (50-81) | 52 (52-82) | 49.5 (40-52) | 0.01     |
| LTL <10th percentile, N | 3 (4%) | 0 | 0 | 3 (9%) | 0.11     |

| COMORBIDITIES | | | | | |
| Hypertension | 41 (54%) | 20 (65%) | 5 (38%) | 16 (50%) | 0.24     |
| Diabetes | 25 (33%) | 12 (41%) | 6 (46%) | 7 (22%) | 0.20     |
| COPD | 4 (5%) | 1 (3%) | 0 | 3 (9%) | 0.36     |
| Asthma | 18 (27%) | 8 (26%) | 4 (31%) | 6 (19%) | 0.65     |
| Heart Disease | 2 (3%) | 1 (3%) | 1 (8%) | 0 | 0.17     |
| Chronic Kidney Disease | 7 (9%) | 5 (16%) | 0 | 2 (6%) | 0.29     |
| Smoking Status | | | | |  |
| Ever | 31 (41%) | 16 (52%) | 4 (31%) | 11 (34%) | 0.27     |
| Active | 2 (3%) | 1 (3%) | 0 | 1 (2%) | 0.81     |
| Pack Years (IQR) | 15 (5-20) | 15 (5-20) | 4.25 (1 - 13.75) | 20 (8-22.5) | 0.34     |

| CLINICAL FACTORS | | | | | |
| Admission SOFA Score, mean (SD) | 4.1 (2.4) | 2.9 (1.7) | 4.5 (3.4) | 5.3 (2.4) | 0.001     |
| Received Steroids | 39 (51%) | 10 (32%) | 5 (38%) | 24 (75%) | 0.002     |
| Received Anti IL-6R blocker** | 17 (22%) | 3 (10%) | 1 (8%) | 13 (41%) | 0.005     |
| Venous thromboembolism (by imaging) | 12 (16%) | 4 (13%) | 1 (8%) | 7 (22%) | 0.42     |
| Received Therapeutic Anticoagulation | 25 (33%) | 6 (19%) | 3 (23%) | 16 (50%) | 0.03     |
| Maximum Oxygen Requirement | <0.001 | | | |  |
| Nasal Cannula | 23 (30%) | 18 (58%) | 4 (31%) | 1 (3%) | 0.001     |
| Non-Rebreather | 17 (22%) | 6 (19%) | 5 (38%) | 6 (19%) | 0.005     |
| NIPPV or HFNC | 4 (5%) | 2 (7%) | 0 | 2 (6%) | 0.42     |
| Mechanical Ventilation | 31 (41%) | 5 (16%) | 4 (31%) | 22 (69%) | 0.03     |
| MV plus ECMO | 1 (1%) | 0 | 1 (3%) | 0 | 0.001     |
| Ventilator Days (IQR) | 30.5 (12-42) | 7 (6-9) | 32.5 (20-41) | 34 (14-42) | <0.001    |
| Hospital days (IQR) | 18 (7-35) | 4 (4-12) | 16 (9-26) | 35 (24-54) | <0.001    |
| Discharge Disposition | | | | | 0.001     |
| Home | 54 (71%) | 29 (94%) | 10 (77%) | 15 (47%) | 0.001     |
| Acute Rehabilitation | 19 (25%) | 1 (3%) | 2 (15%) | 16 (50%) | 0.001     |
| Subacute Rehabilitation | 3 (4%) | 1 (3%) | 1 (8%) | 1 (3%) | 0.001     |
| Home-dwelling at 4 months | 76 (100%) | 31 (100%) | 13 (100%) | 32 (100%) | 1.00     |

| OUTCOMES | | | | | |
| Oxygen use at 4 months | 4 (5%) | 1 (3%) | 2 (15%) | 1 (3%) | 0.25     |
| FVC, % predicted, mean (SD) | 83.6 (19.7) | 87.6 (21.9) | 83.2 (13.6) | 79.8 (19.2) | 0.19     |
| DL(OC), % predicted, mean (SD) | 74.9 (42.1) | 90.5 (24.5) | 74.2 (16.7) | 60.5 (16.6) | <0.001    |
| 6MWD, m, mean (SD) | 364 (98) | 355 (105) | 370 (72) | 370 (103) | 0.82     |
| 6MWD, % predicted, mean (SD) | 68 (18) | 67 (19) | 80 (18) | 65 (16) | 0.06     |
| Change in weight,kg, † median (IQR) | -0.2 (-5.1 - 2.3) | 1.2 (-0.9 - 5.2) | -2.1 (-4.6 - 1.7) | -3.5 (-11.6 - 0.3) | <0.001    |

Data are n (%) unless otherwise specified.
Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; LDH, lactate dehydrogenase; IL-6R, interleukin 6 receptor; NIPPV, non-invasive positive pressure ventilation; HFNC, high-flow nasal cannula.
MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation; FVC, forced vital capacity; DL(CO), diffusion capacity for carbon monoxide; 6MWD, 6 minute walk distance
* Associated examined using Chi-square, ANOVA or Kruskall-Wallis where appropriate
**Either tocilizumab or sarulimab
† Change in weight calculated as weight (kg) measured at 4 month visit minus weight documented at hospital admission.
Table S2. Prevalence of HRCT Abnormalities.

|                      | Total (n=76) | Non-Fibrotic Patterns (n=13) | Fibrotic-Like Patterns (n=32) |
|----------------------|--------------|------------------------------|------------------------------|
| Any Abnormality      | 45 (59%)     | 0                            | 1 (3%)                       |
| Non-Fibrotic Abnormalities*: |              |                              |                              |
| Intraparenchymal opacities | 1 (1%)       | 0                            | 1 (3%)                       |
| Ground glass opacities    | 33 (43%)     | 13 (100%)                    | 20 (62%)                     |
| Nonemphysematous cysts   | 1 (1%)       | 0                            | 1 (3%)                       |
| Diffuse centrilobular nodules | 0            | 0                            | 0                            |
| Fibrotic Abnormalities*: |              |                              |                              |
| Reticulations          | 30 (39%)     | 0                            | 30 (94%)                     |
| Honeycombing           | 1 (1%)       | 0                            | 1 (3%)                       |
| Traction Bronchiectasis | 21 (28%)     | 0                            | 21 (66%)                     |

HRCT: high resolution computed tomography
*patterns are not mutually exclusive and participants with fibrotic-like patterns can also have non-fibrotic patterns.
Table S3. Demographics and Clinical Factors Between those with and without Fibrotic-Like Patterns on CT Scan

|                                | Total   | Normal or Non-Fibrotic Pattern | Fibrotic-Like Pattern | p-value* |
|--------------------------------|---------|--------------------------------|-----------------------|----------|
| Number                         | 76      | 44 (58%)                       | 32 (42%)              |          |
| **DEMOGRAPHICS**               |         |                                |                       |          |
| Age, mean (SD)                 | 54.0 (13.7) | 54.4 (13.4)                     | 53.4 (14.2)           | 0.74     |
| Male                           | 45 (61%) | 20 (45%)                       | 25 (78%)              | 0.004    |
| Hispanic ethnicity             | 43 (57%) | 24 (55%)                       | 19 (59%)              | 0.67     |
| Race                           |         |                                |                       | 0.08     |
| White                          | 30 (39%) | 17 (39%)                       | 13 (41%)              |          |
| Black                          | 22 (30%) | 17 (39%)                       | 5 (16%)               |          |
| Asian                          | 1 (1%)   | 0                              | 1 (4%)                |          |
| Other                          | 23 (30%) | 10 (23%)                       | 13 (41%)              |          |
| Body Mass Index (kg/m²), mean (SD) | 32.2 (6.9) | 34.2 (7.0)                     | 30.1 (6.4)           | 0.001    |
| Smoking Status                 |         |                                |                       | 0.32     |
| Ever                           | 31 (41%) | 20 (45%)                       | 11 (34%)              |          |
| Active                         | 2 (3%)   | 1 (2%)                         | 1 (2%)                |          |
| Pack Years (IQR)               | 15 (5-20)| 15 (5-20)                      | 20 (8-22.5)           |          |
| **GENOMIC FACTORS**            |         |                                |                       |          |
| Leukocyte telomere length, percentile (IQR) | 52 (49-68) | 50 (50-79)                     | 49.5 (40-52) | 0.002    |
| LTL <10th percentile, N        | 3 (4%)   | 0                              | 3 (9%)                | 0.04     |
| **CLINICAL FACTORS**           |         |                                |                       |          |
| Admission SOFA Score, mean (SD) | 4.1 (2.4) | 3.2 (2.0)                      | 5.3 (2.4)             | <0.001   |
| Lactate Dehydrogenase U/L, mean (SD) | 597 (295) | 508 (252)                      | 713 (308)             | 0.003    |
| Received Steroids              | 39 (51%) | 15 (34%)                       | 24 (75%)              | 0.001    |
| Received Anti IL-6R blocker**  | 17 (22%) | 4 (9%)                         | 13 (41%)              | 0.001    |
| Venous thromboembolism (by imaging) | 12 (16%) | 5 (11%)                        | 7 (22%)               | 0.21     |
| Received Therapeutic Anticoagulation | 25 (33%) | 9 (20%)                        | 16 (50%)              | 0.007    |
| Required Mechanical Ventilation | 32 (42%) | 9 (20%)                        | 23 (72%)              | <0.001   |
| Ventilator Days, median (IQR)  | 30.5 (12-42) | 0 (0-0)                       | 34 (14-42)           | <0.001   |
| Hospital days, median (IQR)    | 18 (7-35) | 14 (7-39)                      | 35 (14-42)           | <0.001   |

Data are n (%) unless otherwise specified.
Abbreviations: IL-6R, interleukin 6 receptor;
* Associated examined using Chi-square, Students t-test or Wilcoxon rank-sum where appropriate
** Either tocilizumab or sarilumab
Change in weight calculated as weight (kg) measured at 4 month visit minus weight documented at hospital admission.
|                             | Total (N = 32) | None (N = 5)  | Non-Fibrotic Pattern (N = 4) | Fibrotic-Like Pattern (N = 23) | p-value |
|-----------------------------|----------------|---------------|------------------------------|--------------------------------|---------|
| Ventilator support, Days    | 30.5 (12-42)   | 7 (6-9)       | 32.5 (20-41)                 | 34 (14-42)                     | $<0.001$|
| $\text{PaO}_2:\text{FiO}_2^*$, mean (SD) | 166 (78)       | 166 (57)      | 165 (127)                    | 166 (76)                       | 0.99    |
| Sequential Organ Failure Assessment (SOFA) | 5.7 (2.3)      | 3.4 (0.55)    | 7.0 (0.82)                   | 5.9 (2.4)                      | 0.03    |
| Positive End-Expiratory Pressure (cmH2O)* | 15 (12-16)     | 12 (12-14)    | 14 (10-18)                   | 15 (14-16)                     | 0.33    |
| Tidal Volume (per cc/kg ideal body weight)* | 6.4 (5.9-7.3)  | 6.2 (6.1-7.0) | 7.6 (5.6-8.1)                | 6.4 (5.7-6.8)                  | 0.22    |
| Received Steroids (%)       | 20 (62%)       | 2 (40%)       | 1 (25%)                      | 17 (74%)                       | 0.09    |
| Prone Positioning (%)       | 9 (28%)        | 0             | 0                            | 9 (39%)                        | 0.09    |
| Paralysis (%)               | 14 (44%)       | 0             | 1 (25%)                      | 13 (57%)                       | 0.05    |

Abbreviations: $\text{PaO}_2$, partial pressure of arterial oxygen; $\text{FiO}_2$, Fraction of inspired oxygen

*These represent the first measured data following intubation
| Abnormality                        | N (%) |
|-----------------------------------|-------|
| Any Imaging Pattern               | 45 (59%) |
| Fibrotic-Like Pattern             | 32 (42%) |
| Reduced FVC*                      | 27 (36%) |
| Reduced FEV1/FVC*                 | 4 (5%) |
| Reduced DLCO*                     | 40 (53%) |
| Short 6MWD**                      | 59 (78%) |
| Weight Loss >10% baseline         | 14 (18%) |
| Weight Loss >10 lbs†              | 21 (28%) |
| Slow Gait Speed†                  | 18 (24%) |
| Weak Grip†                        | 40 (53%) |
| Decreased Activity†               | 15 (20%) |
| Exhaustion†                       | 15 (20%) |
| UCSD SOBQ ≥ 10                    | 52 (68%) |
| Cough Score ≥ 20‡                 | 11 (14%) |

Abbreviations: FVC, forced vital capacity; FEV1, forced expiratory volume in one second; DLCO, diffusion capacity for carbon monoxide; 6MWD, six-minute walk distance; UCSD SOBQ, University of California San Diego Shortness of Breath Questionnaire.

* A reduced FVC or FEV1/FVC was defined as being below the lower limit of normal (LLN) for each subject.

** A short 6MWD was defined as being <80 percent of their predicted values.

† Fried frailty domain criteria (see Supplemental methods).

‡ Cough visual analog score
### Table S6. Associations between independent variables of interest and fibrotic-like patterns in multivariable logistic regression

| Variable                                | OR   | 95% CI     | p-value |
|-----------------------------------------|------|------------|---------|
| Male Sex                                | 1.28 | 0.28 - 5.95| 0.75    |
| BMI, m²/kg                               | 0.91 | 0.80 - 1.04| 0.13    |
| Age-Adjusted Telomere length’           | 1.35 | 1.06 - 1.72| 0.01    |
| SOFA Score**                            | 1.49 | 1.17 - 1.89| 0.002   |
| Lactate Dehydrogenase, U/L              | 1.24 | 1.08 - 1.43| 0.003   |
| Days on Mechanical Ventilation          | 1.07 | 1.03 - 1.12| <0.001  |

BMI: body mass index; SOFA: sequential organ failure assessment

All analyses are adjusted for propensity scores that comprised age, sex, race, BMI, admission SOFA score, admission LDH, telomere length, ventilator days and days between positive COVID PCR and CT scan.

‘ per 10% decrease in telomere length

‘’ per 50-point increase in variable
Table S7. Spearman correlation between SOFA score, ventilator days, and age-adjusted percent telomere length and covariables before and after covariate-balancing propensity score.

| SOFA score, hospital admission | Pre-CBPS weighting | Post-CBPS weighting |
|-------------------------------|--------------------|---------------------|
| Age                           | 0.027              | 0.140               |
| Sex                           | 0.316              | 0.080               |
| Time from COVID+ nasal swab to CT scan, in days | 0.220              | 0.166               |
| Black/African American        | -0.187             | -0.027              |
| Hispanic                      | 0.249              | 0.037               |
| Other                         | -0.010             | -0.017              |
| BMI                           | -0.178             | -0.004              |
| Smoking, pack-years           | 0.046              | 0.067               |
| Steroid therapy               | 0.363              | 0.190               |
| Telomere length               | -0.333             | -0.122              |
| Ventilator days               | 0.531              | 0.166               |

| Ventilator Days               | Pre-CBPS weighting | Post-CBPS weighting |
|-------------------------------|--------------------|---------------------|
| Age                           | -0.189             | -0.166              |
| Sex                           | 0.326              | 0.159               |
| Time from COVID+ nasal swab to CT scan, in days | 0.293              | 0.128               |
| Black/African American        | -0.218             | -0.064              |
| Hispanic                      | 0.235              | 0.128               |
| Other                         | 0.068              | -0.044              |
| BMI                           | -0.173             | -0.046              |
| Smoking, pack-years           | -0.117             | -0.040              |
| Steroid therapy               | 0.125              | 0.175               |
| Telomere length               | -0.117             | -0.101              |
| SOFA score, day of admission  | 0.532              | 0.273               |

| Telomere Length (TL)          | Pre-CBPS weighting | Post-CBPS weighting |
|-------------------------------|--------------------|---------------------|
| Age                           | -0.074             | -0.015              |
| Sex                           | -0.046             | -0.045              |
| Time from COVID+ nasal swab to CT scan, in days | -0.12              | -0.075              |
| Black/African American        | -0.179             | 0.053               |
| Hispanic                      | -0.173             | -0.039              |
| Other                         | 0.088              | -0.001              |
| BMI                           | 0.106              | 0.061               |
| Smoking, pack-years           | -0.117             | -0.006              |
| Steroid therapy               | -0.142             | -0.035              |
| SOFA, day of admission        | -0.333             | -0.108              |
| Ventilator days               | -0.117             | -0.054              |
Figure S1. Study flow diagram
Figure S2. Continuous association of the natural log of the percent of Ground Glass Opacity (GGO) pattern as measured by Adaptive Multiple Features Method (AMFM) and the presence of any radiographic abnormality (left) and percent of Ground Glass Reticulation (GGR) pattern via AMFM and fibrotic-like pattern (right) using generalized additive models with LOESS smoothers. Both models are adjusted for age, sex, race/ethnicity and BMI.
Figure S3. Sensitivity of the continuous association of fibrotic-like patterns on CT with SOFA score (top left), lactate dehydrogenase (top right), ventilator days (bottom left) and age-adjusted leukocyte telomere length percentile (bottom right) using generalized additive models with LOESS smoothers. Each model is adjusted for a common set of potential confounders (age, sex, race/ethnicity, days since infection, body mass index, pack-years of smoking and treatment with steroids while hospitalized), but not the other independent variables (SOFA score, LDH, days of mechanical ventilation, telomere length).
Figure S4. Sensitivity of the continuous association of fibrotic patterns on CT as defined by the presence of traction bronchiectasis or honeycombing with SOFA score (top left), lactate dehydrogenase (top right), ventilator days (bottom left) and age-adjusted leukocyte telomere length percentile (bottom right) using generalized additive models with LOESS smoothers. Each model is adjusted for a common set of potential confounders (age, sex, race/ethnicity, days since infection, body mass index, pack-years of smoking and treatment with steroids while hospitalized) and the other independent variables (SOFA score, LDH, days of mechanical ventilation, telomere length). The magnitude and shape of the associations do not appear meaningfully different from the main analysis where fibrotic-like radiographic abnormalities are defined as the presence of reticulations, traction bronchiectasis, or honeycombing.
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SUPPLEMENTAL MATERIALS

Pulmonary Fibrosis after COVID-19 is Associated with Severity of Illness and Blood Leukocyte Telomere Length

Supplemental Methods.

Table S1. Demographic and clinical features of COVID-19 survivors.

Table S2. Prevalence of HRCT abnormalities.

Table S3. Demographics and Clinical Factors between those with and without fibrotic patterns.

Table S4. Clinical Features of COVID-19 Survivors who underwent mechanical ventilation.

Table S5. Prevalence of CT abnormalities, lung function and physical impairment, and respiratory symptoms.

Table S6. Associations between independent variables of interest and fibrotic-like patterns in multivariable logistic regression.

Table S7. Spearman correlations of SOFA score, ventilator days, and age-adjusted percent telomere length with regression model covariables before and after covariate-balancing propensity score.

Figure S1. Study flow diagram

Figure S2. Continuous association of percent Ground Glass Opacity (GGO) and Ground Glass Reticulation (GGR) via adaptive multiple features method lung texture analysis and any radiographic abnormality and fibrotic-like abnormalities.

Figure S3. Sensitivity analysis of the continuous association of fibrotic-like abnormalities with SOFA score, lactate dehydrogenase, days of mechanical ventilation, and age-adjusted leukocyte telomere length (LTL) percentile using generalized additive models with LOESS smoothers.

Figure S4. Sensitivity analysis of the continuous association of fibrotic abnormalities as defined by Fleishner Society position paper with SOFA score, lactate dehydrogenase, days of mechanical ventilation, and age-adjusted leukocyte telomere length (LTL) percentile using generalized additive models with LOESS smoothers.
Supplemental Methods.

Study Design

We conducted a single-center prospective cohort study of adults age 21 years and older hospitalized between March 1, 2020 and May 15, 2020 with a positive SARS-CoV-2 RT-PCR nasopharyngeal swab and who required supplemental oxygen. The Columbia University Irving Medical Center (CUIMC) Institutional Review Board study protocol number is AAAR1916. Participants signed a written informed consent.

Recruitment and Enrollment

We identified prospective patients by chart review to exclude those with pre-existing ILD or a history of lung transplantation. We enrolled prospective participants by calling consecutive subjects meeting eligibility criteria based on their admission date, with sampling weighted to include approximately 50% survivors who underwent mechanical ventilation. We sought to enroll 70-100 participants based upon the capacity of the research team to recruit and assess participants during the 4-month follow-up study period of July and August 2020. Participants ambulated independently prior to hospitalization, did not live in a skilled-care facility prior to hospitalization, required supplemental oxygen therapy during their hospital stay, and were discharged to acute rehabilitation, subacute rehabilitation, or home. All participants were living at home prior to enrollment.

Electronic Medical Record Measurements

We obtained clinical data from the New York Presbyterian-CUIMC clinical data warehouse, which contains electronic data for inpatient and outpatient visits. Patient data included demographics, diagnoses, procedures, medications, laboratory tests, vital signs and ventilator flowsheet data, and other clinical variables. Past medical history diagnoses were retrieved from the hospital admission notes and by using groups of ICD-10 diagnosis codes.
according to the Clinical Classifications Software by the Healthcare Cost and Utilization Project\(^2\).

We calculated the Sequential Organ Failure Assessment (SOFA) score during the first 24 hour of admission\(^3\).

*Chest Computed Tomography*

Non-contrast high resolution chest CT scans (HRCT) were performed at maximal inspiration using either GE VCT 64 or GE Revolution CT750 HD instrument. Two chest radiologists (MS and BD) evaluated the scans for radiographic abnormalities associated with post-acute ARDS\(^4-6\) and COVID-19\(^7-10\), including ground glass opacities, intra-parenchymal opacities, non-emphysematous cysts, centrilobular nodules, reticulations, honeycombing, and traction bronchiectasis. Those with \(\geq 5\%\) involvement of reticulations or honeycombing, or the presence of traction bronchiectasis, were categorized as having fibrotic-like radiographic patterns. All others with \(\geq 5\%\) involvement of a lung quadrant were categorized as having non-fibrotic patterns. The radiographic abnormalities were scored using a semi-quantitative scoring system used by the ARDSnet investigators\(^4\). Radiographic abnormalities were assessed at 5 levels: the aortic arch, 1cm above the diaphragm, and three levels equally spaced between the aortic arch and diaphragm. Each level was divided into four lung quadrants, and scored within each quadrant as: 0=no involvement; 1= <5% involvement; 2= 5–25% involvement; 3=26–49% involvement; 4=50–75% involvement; and 5=greater than 75% involvement. The sum of the quadrant scores at each level was averaged across the five levels to determine the final score (range 0-20). For traction bronchiectasis, an airway abnormality that is difficult to quantify, each level was scored as either 0 or 1 for its absence or presence, respectively, for a maximum score of 5.

In addition to the radiologists’ subjective scoring of fibrotic-like patterns, the University of Iowa imaging lab (Iowa City, IA, USA) used the adaptive multiple features method (AMFM) to
quantify HRCT scans for various lung features, including: ground glass opacity, ground glass-reticular, honeycombing, emphysema, or normal lung\textsuperscript{11}.

**Clinical Measurements**

Pulmonary function tests were performed on one of two pulmonary function machines (NDD EasyOne Pro, Andover MA; Vyaire Medical VMAX Encore, Mettawa IL). Pulmonary function testing and six-minute walk distance (6MWD) were assessed according to established guidelines\textsuperscript{12,13}. Cough was assessed using a 100mm visual analogue scale\textsuperscript{14}. Dyspnea was assessed using the UCSD shortness of breath questionnaire\textsuperscript{15}.

**Frailty Measurements**

We measured the five Fried Frailty domains: gait-speed, grip-strength, weight loss, low activity, and exhaustion. We measured grip-strength, gait-speed, and exhaustion, and using the traditional Cardiovascular Health Study (CHS) methodology\textsuperscript{16}. Weight loss was calculated as the difference between their hospitalization admission weight and the measured weight during the follow up visit. We used the CHS cutoff of a decrease $>$10 lbs. to define the presence of weight loss. We assessed the physical activity domain on the basis of report of activities performed at four-moth follow-up using the Duke Activity Status Index (DASI)\textsuperscript{17} instead of the Minnesota Leisure Time Physical Activity Questionnaire\textsuperscript{18}, the original CHS measure of physical activity, as we have shown that the DASI improves the construct and predictive validity of frailty assessments in acute respiratory failure survivors\textsuperscript{19}. We used previously validated DASI score cutoffs for low activity in older acute respiratory failure survivors (men $\leq 12.5$; women $\leq 10$)\textsuperscript{19}.

Each frailty domain is assigned 1 point if present and 0 points if absent based on the aforementioned cutoffs (range, 0-5). Consistent with CHS methodology, we defined the frailty phenotype as being frail in $\geq 3$ of the five domains.
Genetic and Genomic Measurements

Since neither blood nor genomic DNA was available for all participants from the time of the acute illness, blood was collected from each participant at the 4 month follow-up visit. DNA was isolated from blood leukocytes using the Gentra Puregene Blood kit (Qiagen, Valencia CA). Leukocyte telomere length (LTL) was measured using a quantitative PCR assay and the RotoGene real-type PCR system (Qiagen). The LTL was expressed as a logarithm-transformed ratio of telomere to single-copy gene [ln(T/S)] and this value was compared to LTL from normal control subjects (n=201 unrelated multiethnic individuals from Dallas, TX, ranging in age from 19 to 89 years) to estimate an age-adjusted LTL percentile.

Missing Data

The Glasgow Coma Score, a component of the SOFA score, was missing for nearly all non-ICU patients, and we thus imputed a score of 15 for these participants based on previous literature. Inflammatory markers ESR, CRP, LDH, Ferritin and D-dimer, had 6-12% missingness. We used the MICE function in R(v3.5.1) to perform multiple imputation using predictive mean matching for missing values. There were six participants that could not perform the 6-minute walk test because they were non-ambulatory and one whose baseline heart rate was too high to safely perform the test. For the six participants who were non-ambulatory, we imputed 0 and ran a complete case analysis excluding the last participant. Three participants were unable to produce acceptable or reproducible DLCO measure. Therefore, we ran a complete case analyses using only participants with complete PFT data.

Statistical Analyses

We examined unadjusted associations of clinical and biomarker characteristics with no abnormalities, non-fibrotic pattern or fibrotic-like pattern using analysis of variance (ANOVA),
Kruskal Wallis, or chi-squared tests. We calculated correlation coefficients between continuous data using Spearman’s method. We examined adjusted associations of fibrotic-like patterns with the hypothesized and biologically plausible independent variables that were associated with fibrotic-like patterns in unadjusted analyses. We used generalized covariate balanced propensity scores (CBPS) to adjust for potential confounders as has been done in prior studies. To avoid model overparameterization. We generated propensity scores predicting each of the independent variables of interest (Table S6) using the CBPS function in R(v3.5.1). To do so, we calculated CBPS for each independent variable by regressing it on a set of potential confounders. For all the independent variables, we included a list of common confounders, including age, sex, race/ethnicity, days since infection, body mass index, pack-years of smoking, and treatment with steroids while hospitalized in the generation of the CBPS. In addition, each CBPS score was generated with the other three independent variables of interest. For example, the SOFA CBPS included the common confounders (age, sex, etc.) plus LDH, days of mechanical ventilation, and telomere length. Thus, each GAM has only two variables: (1) the independent variable of interest and (2) the CBPS score for that variable, with collectively controls for the aforementioned potential confounders.

In the GAMs, we did not assume linear associations between continuous independent variables and risk of fibrotic-like abnormalities on CT scan, and instead estimated associations by a nonparametric locally weighted smoothing spline (LOESS). For lab values like LDH, we removed outliers beyond 2 standard deviations for the analysis. For independent variables without statistically significant non-linear associations with fibrotic-like abnormalities in the GAMs, we estimated adjusted odds ratios using logistic regression models. Conventional residuals and quantile residuals showed no substantive bias, had a mean of zero, and demonstrated constant variance across the predicated values, predictors and propensity scores.

Since LTL may increase severity of illness, and since LTL may be affected by critical illness, we conducted sensitivity analyses: one estimating associations of LTL, admission
SOFA score, LDH, and duration of mechanical ventilation with fibrotic-like patterns without adjusting for the other three independent variables. The second sensitivity analysis was performed with a more conservative definition of fibrosis that comprised only traction bronchiectasis and honeycombing. Covariates were found to be balanced in all propensity scores (see Table S7). Plots Analysis were performed using Stata/IC v16 (StataCorp) and R, v3.5.1.
**Table S1. Demographic and clinical features of COVID-19 survivors.**

|                        | Total  | Normal CT chest | Non-Fibrotic pattern | Fibrotic-like pattern | p-value* |
|------------------------|--------|-----------------|----------------------|-----------------------|----------|
| **Number**             | 76     | 31 (41%)        | 13 (17%)             | 32 (42%)              |          |
| **DEMOGRAPHICS**       |        |                 |                      |                       |          |
| Age, mean (SD)         | 54.0 (13.7) | 51.8 (13.7) | 60.6 (10.8)         | 53.4 (14.2)           | 0.14     |
| Male (%)               | 45 (61%) | 16 (52%)        | 4 (31%)              | 25 (78%)              | 0.007    |
| Hispanic ethnicity     | 43 (57%) | 14 (45%)        | 10 (77%)             | 19 (59%)              | 0.14     |
| **Race**               |        |                 |                      |                       | 0.17     |
| White                  | 30 (39%) | 13 (42%)        | 4 (31%)              | 13 (41%)              |          |
| Black                  | 22 (30%) | 13 (42%)        | 4 (31%)              | 5 (16%)               |          |
| Asian                  | 1 (1%)  | 0               | 0                    | 1 (4%)                |          |
| Other                  | 23 (30%) | 5 (16%)         | 5 (38%)              | 13 (41%)              |          |
| Body Mass Index (kg/m²), mean (SD) |            | 32.2 (6.9) | 34.2 (7.8)         | 32.7 (4.6)            | 30.1 (6.4) | 0.07 |
| **GENOMIC FACTORS**    |        |                 |                      |                       |          |
| Leukocyte telomere length, percentile (IQR) | 52 (49-68) | 52 (50-81) | 52 (52-82)         | 49.5 (40-52)          | 0.01     |
| LTL <10th percentile, N | 3 (4%)  | 0               | 0                    | 3 (9%)                | 0.11     |
| **COMORBIDITIES**      |        |                 |                      |                       |          |
| Hypertension           | 41 (54%) | 20 (65%)        | 5 (38%)              | 16 (50%)              | 0.24     |
| Diabetes               | 25 (33%) | 12 (41%)        | 6 (46%)              | 7 (22%)               | 0.20     |
| COPD                   | 4 (5%)  | 1 (3%)          | 0                    | 3 (9%)                | 0.36     |
| Asthma                 | 18 (27%) | 8 (26%)         | 4 (31%)              | 6 (19%)               | 0.65     |
| Heart Disease          | 2 (3%)  | 1 (3%)          | 1 (8%)               | 0                     | 0.17     |
| Chronic Kidney Disease | 7 (9%)  | 5 (16%)         | 0                    | 2 (6%)                | 0.29     |
| Smoking Status         |        |                 |                      |                       |          |
| Ever                   | 31 (41%) | 16 (52%)        | 4 (31%)              | 11 (34%)              | 0.27     |
| Active Pack Years (IQR) | 15 (5-20) | 15 (5-20) | 4.25 (1 - 13.75)    | 20 (8-22.5)           | 0.34     |
| **CLINICAL FACTORS**   |        |                 |                      |                       |          |
| Admission SOFA Score, mean (SD) | 4.1 (2.4) | 2.9 (1.7) | 4.5 (3.4)         | 5.3 (2.4)             |          |
| Received Steroids      | 39 (51%) | 10 (32%)        | 5 (38%)              | 24 (75%)              | 0.002    |
| Received Anti IL-6R blocker** | 17 (22%) | 3 (10%) | 1 (8%)            | 13 (41%)              | 0.005    |
| Venous thromboembolism (by imaging) | 12 (16%) | 4 (13%) | 1 (8%)            | 7 (22%)               | 0.42     |
| Received Therapeutic Anticoagulation | 25 (33%) | 6 (19%) | 3 (23%)         | 16 (50%)              | 0.03     |
| Maximum Oxygen Requirement |        |                 |                      |                       | <0.001   |
| Nasal Cannula          | 23 (30%) | 18 (58%)        | 4 (31%)              | 1 (3%)                |          |
| Non-Rebreather         | 17 (22%) | 6 (19%)         | 5 (38%)              | 6 (19%)               |          |
| NIPPV or HFNC          | 4 (5%)  | 2 (7%)          | 0                    | 2 (6%)                |          |
| Mechanical Ventilation | 31 (41%) | 5 (16%)         | 4 (31%)              | 22 (69%)              |          |
| MV plus ECMO           | 1 (1%)  | 0               | 0                    | 1 (3%)                |          |
| Ventilator Days (IQR)  | 30.5 (12-42) | 7 (6-9) | 32.5 (20-41)      | 34 (14-42)            | <0.001   |
| Hospital days (IQR)    | 18 (7-35) | 4 (4-12) | 16 (9-26)         | 35 (24-54)            | <0.001   |
| **OUTCOMES**           |        |                 |                      |                       |          |
| Oxygen use at 4 months | 4 (5%)  | 1 (3%)          | 2 (15%)              | 1 (3%)                | 0.25     |
| 6MWD, m, mean (SD)     | 364 (98) | 355 (105) | 370 (72)          | 370 (103)             | 0.82     |
| 6MWD, % predicted, mean (SD) | 68 (18) | 67 (19) | 80 (18)          | 65 (16)               | 0.06     |
| Change in weight,kg, † median (IQR) | -0.2 (-5.1 - 2.3) | 1.2 (-0.9 - 5.2) | -2.1 (-4.6 - 1.7) | -3.5 (-11.6 - 0.3) | <0.001 |

Data are n (%) unless otherwise specified.

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; LDH, lactate dehydrogenase; IL-6R, interleukin 6 receptor; NIPPV, non-invasive positive pressure ventilation; HFNC, high-flow nasal cannula.
MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation; FVC, forced vital capacity; DL(CO), diffusion capacity for carbon monoxide; 6MWD, 6 minute walk distance

* Associated examined using Chi-square, ANOVA or Kruskall-Wallis where appropriate
** Either tocilizumab or sarulimab
† Change in weight calculated as weight (kg) measured at 4 month visit minus weight documented at hospital admission.
Table S2. Prevalence of HRCT Abnormalities.

| Abnormality                        | Total (n=76) | Non-Fibrotic Patterns (n=13) | Fibrotic-Like Patterns (n=32) |
|------------------------------------|--------------|-----------------------------|------------------------------|
| Any Abnormality                    | 45 (59%)     |                             |                              |
| Non-Fibrotic Abnormalities*        |              |                             |                              |
| Intraparenchymal opacities         | 1 (1%)       | 0                           | 1 (3%)                       |
| Ground glass opacities             | 33 (43%)     | 13 (100%)                   | 20 (62%)                     |
| Nonemphysematous cysts             | 1 (1%)       | 0                           | 1 (3%)                       |
| Diffuse centrilobular nodules      | 0            | 0                           | 0                            |
| Fibrotic Abnormalities*            |              |                             |                              |
| Reticulations                      | 30 (39%)     | 0                           | 30 (94%)                     |
| Honeycombing                       | 1 (1%)       | 0                           | 1 (3%)                       |
| Traction Bronchiectasis            | 21 (28%)     | 0                           | 21 (66%)                     |

HRCT: high resolution computed tomography

* patterns are not mutually exclusive and participants with fibrotic-like patterns can also have non-fibrotic patterns.
### Table S3. Demographics and Clinical Factors Between those with and without Fibrotic-Like Patterns on CT Scan

|                           | Total         | Normal or Non-Fibrotic Pattern | Fibrotic-Like Pattern | p-value* |
|---------------------------|---------------|-------------------------------|-----------------------|----------|
| Number                    | 76            | 44 (58%)                      | 32 (42%)             |          |
| **DEMOGRAPHICS**          |               |                               |                       |          |
| Age, mean (SD)            | 54.0 (13.7)   | 54.4 (13.4)                   | 53.4 (14.2)           | 0.74     |
| Male                      | 45 (61%)      | 20 (45%)                      | 25 (78%)             | 0.004    |
| Hispanic ethnicity        | 43 (57%)      | 24 (55%)                      | 19 (59%)             | 0.67     |
| Race                      |               |                               |                       | 0.08     |
| White                     | 30 (39%)      | 17 (39%)                      | 13 (41%)             |          |
| Black                     | 22 (30%)      | 17 (39%)                      | 5 (16%)              |          |
| Asian                     | 1 (1%)        | 0                             | 1 (4%)               |          |
| Other                     | 23 (30%)      | 10 (23%)                      | 13 (41%)             |          |
| Body Mass Index (kg/m²), mean (SD) | 32.2 (6.9)   | 34.2 (7.0)                    | 30.1 (6.4)           | 0.001    |
| Smoking Status            |               |                               |                       | 0.32     |
| Ever                      | 31 (41%)      | 20 (45%)                      | 11 (34%)             |          |
| Active                    | 2 (3%)        | 1 (2%)                        | 1 (2%)               |          |
| Pack Years (IQR)          | 15 (5-20)     | 15 (5-20)                     | 20 (8-22.5)          |          |
| **GENOMIC FACTORS**       |               |                               |                       |          |
| Leukocyte telomere length, percentile (IQR) | 52 (49-68)   | 50 (50-79)                    | 49.5 (40-52)         | 0.002    |
| LTL <10th percentile, N   | 3 (4%)        | 0                             | 3 (9%)               | 0.04     |
| **CLINICAL FACTORS**      |               |                               |                       |          |
| Admission SOFA Score, mean (SD) | 4.1 (2.4)    | 3.2 (2.0)                     | 5.3 (2.4)            | <0.001   |
| Lactate Dehydrogenase U/L, mean (SD) | 597 (295)   | 508 (252)                     | 713 (308)            | 0.003    |
| Received Steroids         | 39 (51%)      | 15 (34%)                      | 24 (75%)             | 0.001    |
| Received Anti IL-6R blocker** | 17 (22%)   | 4 (9%)                        | 13 (41%)             | 0.001    |
| Venous thromboembolism (by imaging) | 12 (16%)    | 5 (11%)                       | 7 (22%)              | 0.21     |
| Received Therapeutic Anticoagulation | 25 (33%)   | 9 (20%)                       | 16 (50%)             | 0.007    |
| Required Mechanical Ventilation | 32 (42%)    | 9 (20%)                       | 23 (72%)             | <0.001   |
| Ventilator Days, median (IQR) | 30.5 (12-42) | 0 (0-0)                       | 34 (14-42)           | <0.001   |
| Hospital days, median (IQR) | 18 (7-35)   | 14 (7-39)                     | 35 (14-42)           | <0.001   |

Data are n (%) unless otherwise specified. Abbreviations: IL-6R, interleukin 6 receptor; * Associated examined using Chi-square, Students t-test or Wilcoxon rank-sum where appropriate ** Either tocilizumab or sarilimab

Change in weight calculated as weight (kg) measured at 4 month visit minus weight documented at hospital admission.
|                                | Total (N = 32) | None (N = 5) | Non-Fibrotic Pattern (N = 4) | Fibrotic-Like Pattern (N = 23) | p-value  |
|--------------------------------|----------------|-------------|-----------------------------|-------------------------------|----------|
| Ventilator support, Days       | 30.5 (12-42)   | 7 (6-9)     | 32.5 (20-41)                | 34 (14-42)                    | <0.001   |
| PaO$_2$:FiO$_2^*$, mean (SD)   | 166 (78)       | 166 (57)    | 165 (127)                   | 166 (76)                      | 0.99     |
| Sequential Organ Failure       | 5.7 (2.3)      | 3.4 (0.55)  | 7.0 (0.82)                  | 5.9 (2.4)                     | 0.03     |
| Assessment (SOFA)              |                |             |                             |                               |          |
| Positive End-Expiratory        | 15 (12-16)     | 12 (12-14)  | 14 (10-18)                  | 15 (14-16)                    | 0.33     |
| Pressure (cmH$_2$O)$^*$         |                |             |                             |                               |          |
| Tidal Volume (per cc/kg ideal  | 6.4 (5.9-7.3)  | 6.2 (6.1-7.0)| 7.6 (5.6-8.1)               | 6.4 (5.7-6.8)                 | 0.22     |
| body weight)$^*$               |                |             |                             |                               |          |
| Received Steroids (%)          | 20 (62%)       | 2 (40%)     | 1 (25%)                     | 17 (74%)                      | 0.09     |
| Prone Positioning (%)          | 9 (28%)        | 0           | 0                           | 9 (39%)                       | 0.09     |
| Paralysis (%)                  | 14 (44%)       | 0           | 1 (25%)                     | 13 (57%)                      | 0.05     |

Abbreviations: PaO$_2$, partial pressure of arterial oxygen; FiO$_2$, Fraction of inspired oxygen

$^*$These represent the first measured data following intubation
Table S5. Prevalence of CT abnormalities, lung function, physical impairment, and respiratory symptoms.

| Abnormality                        | N (%) |
|------------------------------------|-------|
| Any Imaging Pattern                | 45 (59%) |
| Fibrotic-Like Pattern              | 32 (42%) |
| Reduced FVC*                       | 27 (36%) |
| Reduced FEV1/FVC*                  | 4 (5%) |
| Reduced DLCO*                      | 40 (53%) |
| Short 6MWD**                       | 59 (78%) |
| Weight Loss >10% baseline          | 14 (18%) |
| Weight Loss >10 lbs†               | 21 (28%) |
| Slow Gait Speed†                   | 18 (24%) |
| Weak Grip†                         | 40 (53%) |
| Decreased Activity†                | 15 (20%) |
| Exhaustion†                        | 15 (20%) |
| UCSD SOBQ ≥ 10                     | 52 (68%) |
| Cough Score ≥ 20‡                  | 11 (14%) |

Abbreviations: FVC, forced vital capacity; FEV1, forced expiratory volume in one second; DLCO, diffusion capacity for carbon monoxide; 6MWD, six-minute walk distance; UCSD SOBQ, University of California San Diego Shortness of Breath Questionnaire.

* A reduced FVC or FEV1/FVC was defined as being below the lower limit of normal (LLN) for each subject.
** A short 6MWD was defined as being <80 percent of their predicted values.
† Fried frailty domain criteria (see Supplemental methods).
‡ Cough visual analog score
### Table S6. Associations between independent variables of interest and fibrotic-like patterns in multivariable logistic regression

| Variable                                      | OR   | 95% CI       | p-value |
|-----------------------------------------------|------|--------------|---------|
| Male Sex                                      | 1.28 | 0.28 - 5.95  | 0.75    |
| BMI, m²/kg                                    | 0.91 | 0.80 - 1.04  | 0.13    |
| Age-Adjusted Telomere length\(^\ast\)        | 1.35 | 1.06 - 1.72  | 0.01    |
| SOFA Score\(^\ast\)                          | 1.49 | 1.17 - 1.89  | 0.002   |
| Lactate Dehydrogenase, U/L                    | 1.24 | 1.08 - 1.43  | 0.003   |
| Days on Mechanical Ventilation               | 1.07 | 1.03 - 1.12  | <0.001  |

BMI: body mass index; SOFA: sequential organ failure assessment

All analyses are adjusted for propensity scores that comprised age, sex, race, BMI, admission SOFA score, admission LDH, telomere length, ventilator days and days between positive COVID PCR and CT scan, 

\(^\ast\) per 10% decrease in telomere length

\(^\ast\) per 50-point increase in variable
Table S7. Spearman correlation between SOFA score, ventilator days, and age-adjusted percent telomere length and covariables before and after covariate-balancing propensity score.

| SOFA score, hospital admission | Pre-CBPS weighting | Post-CBPS weighting |
|--------------------------------|--------------------|---------------------|
| Age                            | 0.027              | 0.140               |
| Sex                            | 0.316              | 0.080               |
| Time from COVID+ nasal swab to CT scan, in days | 0.220         | 0.166               |
| Black/African American          | -0.187             | -0.027              |
| Hispanic                        | 0.249              | 0.037               |
| Other                          | -0.010             | -0.017              |
| BMI                            | -0.178             | -0.004              |
| Smoking, pack-years             | 0.046              | 0.067               |
| Steroid therapy                | 0.363              | 0.190               |
| Telomere length                | -0.333             | -0.122              |
| Ventilator days                | 0.531              | 0.166               |

| Ventilator Days                | Pre-CBPS weighting | Post-CBPS weighting |
|--------------------------------|--------------------|---------------------|
| Age                            | -0.189             | -0.166              |
| Sex                            | 0.326              | 0.159               |
| Time from COVID+ nasal swab to CT scan, in days | 0.293         | 0.128               |
| Black/African American          | -0.218             | -0.064              |
| Hispanic                        | 0.235              | 0.128               |
| Other                          | 0.068              | -0.044              |
| BMI                            | -0.173             | -0.046              |
| Smoking, pack-years             | -0.117             | -0.040              |
| Steroid therapy                | 0.125              | 0.175               |
| Telomere length                | -0.117             | -0.101              |
| SOFA score, day of admission   | 0.532              | 0.273               |

| Telomere Length (TL)           | Pre-CBPS weighting | Post-CBPS weighting |
|--------------------------------|--------------------|---------------------|
| Age                            | -0.074             | -0.015              |
| Sex                            | -0.046             | -0.045              |
| Time from COVID+ nasal swab to CT scan, in days | -0.12          | -0.075              |
| Black/African American          | -0.179             | 0.053               |
| Hispanic                        | -0.173             | -0.039              |
| Other                          | 0.088              | -0.001              |
| BMI                            | 0.106              | 0.061               |
| Smoking, pack-years             | -0.117             | -0.006              |
| Steroid therapy                | -0.142             | -0.035              |
| SOFA, day of admission         | -0.333             | -0.108              |
| Ventilator days                | -0.117             | -0.054              |
Figure S1. Study flow diagram
Figure S2. Continuous association of the natural log of the percent of Ground Glass Opacity (GGO) pattern as measured by Adaptive Multiple Features Method (AMFM) and the presence of any radiographic abnormality (left) and percent of Ground Glass Reticulation (GGR) pattern via AMFM and fibrotic-like pattern (right) using generalized additive models with LOESS smoothers. Both models are adjusted for age, sex, race/ethnicity and BMI.
Figure S3. Sensitivity of the continuous association of fibrotic-like patterns on CT with SOFA score (top left), lactate dehydrogenase (top right), ventilator days (bottom left) and age-adjusted leukocyte telomere length percentile (bottom right) using generalized additive models with LOESS smoothers. Each model is adjusted for a common set of potential confounders (age, sex, race/ethnicity, days since infection, body mass index, pack-years of smoking and treatment with steroids while hospitalized), but not the other independent variables (SOFA score, LDH, days of mechanical ventilation, telomere length).
Figure S4. Sensitivity of the continuous association of fibrotic patterns on CT as defined by the presence of traction bronchiectasis or honeycombing with SOFA score (top left), lactate dehydrogenase (top right), ventilator days (bottom left) and age-adjusted leukocyte telomere length percentile (bottom right) using generalized additive models with LOESS smoothers. Each model is adjusted for a common set of potential confounders (age, sex, race/ethnicity, days since infection, body mass index, pack-years of smoking and treatment with steroids while hospitalized) and the other independent variables (SOFA score, LDH, days of mechanical ventilation, telomere length). The magnitude and shape of the associations do not appear meaningfully different from the main analysis where fibrotic-like radiographic abnormalities are defined as the presence of reticulations, traction bronchiectasis, or honeycombing.
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