Improved pulmonary function and exercise tolerance despite persistent pulmonary fibrosis over 1 year after severe COVID-19 infection

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ABSTRACT

We conducted a prospective single-centre cohort study of 104 multi-ethnic severe COVID-19 survivors from the first wave of the pandemic 15 months after hospitalisation. Of those who were assessed at 4 and 15 months, improvement of ground glass opacities correlated with worsened fibrotic reticulations. Despite a high prevalence of fibrotic patterns (64%), pulmonary function, grip strength, 6 min walk distance and frailty normalised. Overall, dyspnoea, cough and exhaustion did not improve and were not correlated with pulmonary function or radiographic fibrosis at 15 months, suggesting non-respiratory aetiologies. Monitoring persistent, and often subclinical, fibrotic interstitial abnormalities will be needed to determine their potential for future progression.

INTRODUCTION

Cohort studies of COVID-19 survivors demonstrate that incomplete recovery, persistent symptoms and disability are common after the initial infection.[1] Persistent CT scan abnormalities have been documented 1 year following COVID-19 infection, especially among older adults and those who required mechanical ventilation.[2–9] The longitudinal evolution of pulmonary radiographic abnormalities and associations with pulmonary and physical function over time are incompletely characterised. We conducted a prospective multi-ethnic New York City-based single-centre cohort study of severe COVID-19 survivors from the first wave of the pandemic to better characterise cohort characteristics cross-sectionally at 15 months and, for a subset of participants, longitudinal changes from 4 to 15 months.

METHODS

Additional details are included in the online supplemental materials. We enrolled community-dwelling adults aged 21 years and older hospitalised for severe COVID-19 between 1 March and 15 May 2020 who did not have a history of interstitial lung disease or lung transplant.

The 76 participants who participated in a prior follow-up COVID-19 study, in which evaluations were conducted at 4.4 (IQR 4.0–4.8) months,[10] were contacted and invited to return for the follow-up study at 1 year. We sought to enrol additional prospective participants with the same inclusion criteria to increase the total study number to ~100 participants. We enrolled participants meeting eligibility criteria, with sampling weighted to include ~50% who required mechanical ventilation (online supplemental figure S1). Participants underwent non-contrast high-resolution chest CT at maximal inspiration. We performed a semi-quantitative image analysis developed by ARDSnet in an identical manner to that performed at 4 months.[10] We defined fibrotic patterns as the presence of any reticulations, traction bronchiectasis or honeycombing. For the 57 participants with CT scans at 4 and 15 months, two radiologists assessed the proportion of lung affected by radiographic abnormalities and classified the 15-month CT scan as stable, improved or worse. The radiologists were not blinded to the timing of the CT scans and assessed abnormalities together. The University of Iowa imaging lab (Iowa City, Iowa, USA) used the adaptive multiple features method (AMFM) to quantify ground glass opacities (GGO) and ground glass-reticular (GGR) features. We assessed pulmonary function and 6 min walk distance (6MWD). We measured cough, dyspnoea, fatigue and the frailty phenotype with validated questionnaires and methods, and ascertained a battery of potential post-COVID-19 symptoms using the C4R survey.[11] As leucocyte telomere length (LTL) was previously found to be associated with fibrosis 4 months after COVID-19,[10] we measured LTL in an identical manner using a quantitative PCR assay.

We examined unadjusted associations of clinical characteristics, biomarkers and fibrotic patterns in cross-sectional and longitudinal analyses using Mann-Whitney U test, Wilcoxen signed-rank test, McNemar's test and Fischer's exact test. We calculated correlation coefficients between continuous data using Spearman's method. We examined adjusted associations of fibrotic patterns with the independent variables that were correlated in unadjusted analyses using non-parametric and parametric regression with covariate-balanced propensity scores.

RESULTS

The 104 participants had a mean (SD) age of 54.1 (11.1), 59% were male, 60% were Hispanic (online supplemental table S1) and 51% required mechanical ventilation. At a median of 15 (14.2–16.5) months following hospitalisation, 67 participants (64%) had radiographic abnormalities, all of which were characterised as fibrotic

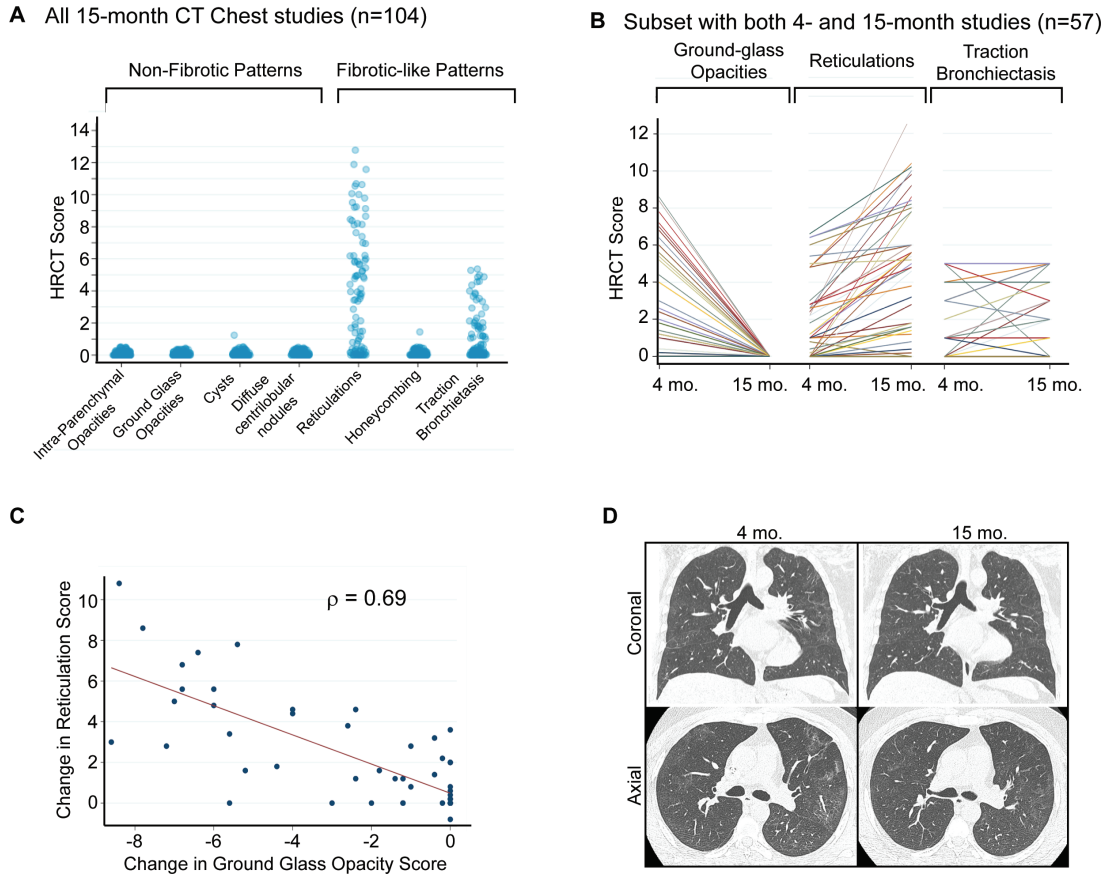

Figure 1 (A) Chest CT pattern scores for 104 post-COVID-19 survivors at 15 months. (B) Change in individual CT pattern scores for 57 individuals who had imaging studies at 4 and 15 months. Each line represents an individual. (C) Scatter plot with a best linear fit line of the change in reticulation scores (y-axis) with the change ground glass opacity scores (x-axis) for individuals who had imaging studies at both 4 and 15 months. Each dot represents an individual. (D) Example of one individual whose CT chest scan showed improvement at 15 months.

patterns: 100% (67/67) with reticulations, 61% (41/67) with traction bronchiectasis and 1% (1/67) with honeycombing (figure 1A; online supplemental table S2). In unadjusted analyses, participants with fibrotic patterns were more likely to be male, have a lower body mass index, have shorter age-adjusted LTLs and have greater severity of illness as indicated by higher admission sequential organ failure assessment (SOFA) scores, higher oxygen requirements, the need for mechanical ventilation and the receipt of steroids. In adjusted analyses, only SOFA score and days of mechanical ventilation were independently associated with fibrotic patterns (online supplemental table S3). The mean (SD) forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO) were 90% (17) and 81% (19) predicted, with 17% and 39% of the cohort having values below the lower limit of normal, respectively (table 1). Fibrotic patterns, or reticulation or traction bronchiectasis individually, at 15 months were not associated with degradations in lung function, 6MWD, frailty or grip strength (online supplemental tables S4 and S5 and online supplemental figure S2). The most common post-COVID-19 symptoms were joint pain (34%), muscle pain (31%), lumbago (30%), dyspnoea (30%), paresthesias (29%), anxiety (29%), trouble sleeping (29%), fatigue (27%) and weight gain (24%). These were not found to be more common in those with lung fibrosis (online supplemental table S6).

Among the 76 participants with 4-month follow-up, 57 agreed to 15-month follow-up. These 57 participants did not appear to differ demographically or clinically from those who declined 15-month follow-up (online supplemental table S7). Compared with all 104 participants with 15-month follow-up, the 57 with additional 4-month follow-up had a similar prevalence and severity of radiographic changes, pulmonary and physical function deficits and symptoms (table 1). In longitudinal analyses, FVC and DLCO, 6MWD, grip strength, physical activity and frailty improved, but validated measures of dyspnoea, cough and exhaustion did not (table 1). Median (IQR) GGO scores decreased from 1 (0–4.4) to 0 (0–0), reticulation scores increased from 0 (0–2.2) to 3.2 (0–6.0) and traction bronchiectasis scores remained stable (figure 1B). A decrease in GGO score, which was inversely correlated with an increase in the reticulation score ($\rho=0.69$, $p<0.001$) (figure 1C), was correlated with increased FVC, DLCO, grip strength and less frailty (table 2, online supplemental figure S3). Radiologists classified 68% of scans as improved (figure 1D). Similarly, AMFM GGO and GGR features decreased; at 15 months, both were inversely correlated with DLCO and 6MWD (online supplemental figure S4, online supplemental table S8).

DISCUSSION

In this prospective multi-ethnic longitudinal cohort of adult survivors of severe COVID-19, 64% have fibrotic patterns >1 year later. These patterns are not correlated with substantial degradations in lung or physical function, frailty, nor symptoms

Table 1 Quantification of functional deficits at 4 months and 1 year

Abnormality	N (%) at 4 months, all (n=76)	N (%) at 15 months, all (n=104)	N (%) for subset with follow-up, at 4 months (n=57)	N (%) for subset with follow-up, at 15 months (n=57)	P value**
Any imaging abnormality	45 (59%)	67 (64%)	36 (63%)	36 (63%)	0.99
Any fibrotic pattern*	32 (42%)	67 (64%)	26 (46%)	36 (63%)	**0.004**
FVC %predicted, mean (SD)	84.0 (19.3)	90.4 (17.2)	83.2 (18.4)	90.2 (17.8)	**0.001**
Reduced FVC	27 (36%)	18 (17%)	21 (37%)	12 (21%)	**0.007**
Reduced FEV_1/FVC	4 (5%)	5 (4%)	1 (1%)	2 (4%)	0.32
DLCO %predicted, mean (SD)	75.7 (23.3)	80.9 (19.1)	75.6 (23.2)	81.4 (18.6)	0.23
Reduced DLCO†	40 (53%)	40 (39%)	33 (58%)	22 (39%)	**0.049**
6MWD, median (IQR)	360 (278–428)	399 (344–369)	365 (278–439)	399 (338–490)	**0.007**
Short 6MWD‡	59 (78%)	58 (56%)	43 (75%)	29 (51%)	**0.011**
Weight loss >10 lb§	21 (28%)	10 (9%)	19 (33%)	7 (12%)	**<0.001**
Slow gait speed§	18 (24%)	12 (12%)	12 (21%)	7 (12%)	0.10
Weak grip§	40 (53%)	46 (44%)	30 (53%)	20 (35%)	**0.03**
Decreased activity§	15 (20%)	1 (1%)	11 (19%)	1 (1%)	**0.002**
Exhaustion§	15 (20%)	31 (29%)	11 (19%)	16 (28%)	0.17
Frail¶	16 (21%)	7 (6%)	12 (21%)	5 (9%)	**0.02**
mMRC dyspnoea score, median (IQR)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	0.35
mMRC dyspnoea score ≥3	8 (12%)	12 (12%)	4 (7%)	6 (11%)	0.72
Cough VAS score, median (IQR)	0 (0–20)	0 (0–20)	1 (0–25)	2 (0–20)	0.64

*Fibrotic patterns include reticulations, traction bronchiectasis or honeycombing.
†Per 2017 ATS/ERS guidelines.
‡<80% predicted based on sex, age, height and weight, per 2017 ATS/ERS guidelines.
§Included measure in the Fried Frailty Phenotype measure. Weight loss >10 lb based on follow-up visit weight - hospital admission weight. Slow gait based on 15-foot walk test CHS criteria. Weak grip based on sex-stratified CHS criteria. Decreased activity based on Duke Activity Status Index scores validated in ICU survivors and lung transplant candidates. Exhaustion based on Center for Epidemiological Disease-Depression survey questions adapted for the Fried Frailty Phenotype assessment in the CHS.
¶As designated by having ≥3/5 Fried Frailty Phenotype domains.
**Exact McNemar's test for comparison of binary outcomes and Wilcoxon signed-rank test for comparison of continuous outcomes.
ATS, American Thoracic Society; BMI, body mass index; CHS, Cardiovascular Health Study; DLCO, diffusion capacity for carbon monoxide; ERS, European Respiratory Society; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; ICU, intensive care unit; mMRC, modified Medical Research Council; 6MWD, 6 min walk distance; VAS, visual analogue scale.

of cough, dyspnoea or fatigue. Our longitudinal analyses of CT scans indicate that, as the GGO resolve, there are improvements in pulmonary and physical function. The persistence and subclinical nature of the fibrotic patterns suggests that long COVID respiratory symptoms may stem from extrapulmonary aetiologies, such as cardiovascular or neuromuscular dysfunction.

While our study of severe COVID-19 survivors is derived from a single-centre New York City-based cohort, the type, severity and prevalence of fibrotic patterns at 15 months are consistent with other 1-year follow-up cohorts from Europe and Asia, where 40%–75% had fibrotic abnormalities that were related to mild reductions in diffusion capacity, and not consistently related to restrictive or obstructive ventilatory defects, reduced exercise tolerance or dyspnoea.[2 4 10 12 13] There is a trend that shorter age-adjusted LTL is independently associated with fibrotic patterns at 1 year, consistent with other studies that have shown its association with adverse COVID-19 outcomes.[14]

We acknowledge that this study, like others, is limited by the unknown radiographic patterning of individuals prior to COVID-19. It is also limited by sample size for the subset with repeated

Table 2 Correlations of changes in chest CT abnormalities with measures of physical function, pulmonary function and dyspnoea

	Change in grip			Change in frailty score			Change in SOBQ score		
	R^2	r	P value	R^2	r	P value	R^2	r	P value
GGO score change	0.22	−0.46	**0.0003**	0.22	0.47	**0.0002**	0.00	0.05	0.74
Reticulation score change	0.25	0.50	**0.0001**	0.14	−0.37	**0.004**	0.00	−0.04	0.77
Traction bronchiectasis score change	0.00	0.02	0.87	0.04	−0.19	0.16	0.00	−0.04	0.77
	Change in FVC			**Change in DLCO**			**Change in 6MWD**		
	R^2	r	P value	R^2	r	P value	R^2	r	P value
GGO score change	0.17	−0.41	**0.002**	0.13	−0.36	**0.01**	0.00	−0.05	0.72
Reticulation score change	0.25	0.50	**<0.0001**	0.04	0.19	0.17	0.01	−0.11	0.42
Traction bronchiectasis score change	0.01	0.08	0.54	0.05	−0.22	0.11	0.00	−0.05	0.72

Spearman's correlations obtained between individuals with longitudinal data, n=57.
See online supplemental figure S3 for scatter plots of data that constitute the observed correlations.
DLCO, diffusion capacity for carbon monoxide; FVC, forced vital capacity; GGO, ground glass opacities; 6MWD, 6 min walk distance; SOBQ, Shortness of Breath Questionnaire.

evaluations. Given our limited sample size, these findings should be considered preliminary and hypothesis generating.

In the longitudinal analysis, our novel finding indicates that resolving GGO is correlated with increased reticulation scores and improved lung function and walk distance. This suggests that GGOs may represent lung and systemic inflammation following viral illness, thus, partly contributing to a long COVID subphenotype.[15] We find that the fibrotic patterns at 15 months appear to be residual remnants of COVID-19. In that they are often subclinical, it remains to be seen how they might be similar to interstitial lung abnormalities described in population cohorts.[16 17] Accordingly, continued longitudinal monitoring of lung function and future investigations into the histopathology of residual COVID-19 lung abnormalities are needed to determine which patients have the greatest risk of future progression and need for treatment.

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Contributors CFMcG, MRB and CKG conceptualised the study. CFMcG recruited patients and collected samples and clinical data. MS, BD'S and EAH analysed imaging studies. CFMcG, MRB and CKG performed statistical analysis. CFMcG, MRB and CKG wrote the manuscript.

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Competing interests MS reports relationships with Boehringer Ingelheim, Genetech, Peer View, France Foundation, Bioclinica, AbbVie and Lung Life AI outside the scope of this study. EAH reports a relationship with VIDA Diagnostics. CKG reports a relationship with Boehringer Ingelheim outside the scope of this study.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study was approved by Columbia University Irving Medical Center Institutional Review Board (AAAT5605). Participants gave informed consent to participate in the study before taking part.

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