Radiology

CT Lung Abnormalities after COVID-19 at 3 Months and 1 Year after Hospital Discharge

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Background: Data on the long-term pulmonary sequelae in COVID-19 are lacking.

Purpose: To assess symptoms, functional impairment, and residual pulmonary abnormalities on serial chest CT scans in COVID-19 survivors discharged from hospital at up to 1-year follow-up.

Materials and Methods: Adult patients with COVID-19 discharged between March 2020 and June 2020 were prospectively evaluated at 3 months and 1 year through systematic assessment of symptoms, functional impairment, and thoracic CT scans as part of the PHENOTYPE study, an observational cohort study in COVID-19 survivors. Lung function testing was limited to participants with CT abnormalities and/or persistent breathlessness. Bonferroni correction was used.

Results: Eighty participants (mean age, 59 years ± 13 [SD]; 53 men) were assessed. At outpatient review, persistent breathlessness was reported in 37 of the 80 participants (46%) and cough was reported in 17 (21%). CT scans in 73 participants after discharge (median, 105 days; IQR, 95–141 days) revealed persistent abnormalities in 41 participants (56%), with ground-glass opacification (35 of 73 participants [48%]) and bands (27 of 73 participants [37%]) predominating. Unequivocal signs indicative of established fibrosis (ie, volume loss and/or traction bronchiectasis) were present in nine of 73 participants (12%). Higher admission serum C-reactive protein (in milligrams per liter), fibrinogen (in grams per deciliter), urea (millimoles per liter), and creatinine (micromoles per liter) levels; longer hospital stay (in days); older age (in years); and requirement for invasive ventilation were associated with CT abnormalities at 3-month follow-up. Thirty-two of 41 participants (78%) with abnormal findings at 3-month follow-up CT underwent repeat imaging at a median of 364 days (range, 360–366 days), with 26 (81%) showing further radiologic improvement (median, 18%; IQR, 10%–40%).

Conclusion: CT abnormalities were common at 3 months after COVID-19 but with signs of fibrosis in a minority. More severe acute disease was linked with CT abnormalities at 3 months. However, radiologic improvement was seen in the majority at 1-year follow-up.

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The novel coronavirus, also known as SARS-CoV-2, which causes COVID-19, was designated a pandemic by the World Health Organization in March 2020 (1). As of September 1, 2021, there have been more than 217 million cases and over 4.5 million deaths because of COVID-19 (2).

In addition to substantial mortality, a large proportion of COVID-19 survivors experience persistent morbidity, with symptoms including breathlessness, fatigue, and lowered quality-of-life measures (3–5). These symptoms mirror data from the severe acute respiratory syndrome and Middle East respiratory virus pandemics (6–8).

Breathlessness has been reported in more than half of patients after COVID-19 (3), with female patients younger than 50 years more likely to experience this (9). However, the underlying origin and natural history of pulmonary sequelae after COVID-19 are unclear. One postulate is that respiratory symptoms in survivors might be attributable to pulmonary fibrosis, as reported following other coronavirus (10,11) and influenza (12) pandemics. In this context, fibrosis due to acute respiratory distress syndrome (13,14) or indeed virus-induced initiation or propagation of interstitial lung disease (15,16) is possible.

Radiologic and physiologic abnormalities in COVID-19 survivors have been described, with ground-glass opacification and bands being common findings (17–20). Post-COVID-19 diagnoses of fibrosis have also been made but largely in the absence of histopathologic findings and using a variety of nonstandard radiologic descriptors such as "fibrotic strips" and "irregular lines" with small patient cohorts recovering from severe disease (18,21) and the majority with relatively short-term (up to 6 months) follow-up (22–25).

Abbreviation

mMRC = modified Medical Research Council

Summary

CT abnormalities were common after COVID-19 and linked with disease severity at presentation, but signs of overt fibrosis were uncommon and most morphologic abnormalities regressed over time.

Key Results

- In a prospective study of adults who had been hospitalized for COVID-19, 41 of 73 (56%) had CT abnormalities after a median of 105 days after discharge, most commonly with ground-glass opacities (35 of 73 [48%]).
- Higher serum C-reactive protein ($P = .03$), fibrinogen ($P = .02$), urea ($P = .01$), and creatinine ($P = .03$) levels at admission; length of hospital stay ($P = .008$); age ($P = .04$); and invasive ventilation ($P = .004$) were associated with CT abnormalities.
- Twenty-six of 32 participants (81%) with 1-year CT follow-up had improvement in lung abnormalities.

Studies evaluating serial radiologic changes after COVID-19 are lacking. Therefore, the aims of the present study were to critically review chest CT abnormalities in COVID-19 survivors at up to 1-year follow-up in concert with symptoms and indexes of functional impairment, identify associations with inpatient characteristics, and evaluate serial radiologic findings.

Materials and Methods

Study Design and Participants

PHENOTYPE is a prospective single-center observational study assessing radiologic and clinical recovery in COVID-19 survivors. The study has National Research Ethics Committee approval (IRAS 284497) and is registered at ClinicalTrials.gov (NCT04459351).

Participants aged 18 years and older with confirmed COVID-19, as defined by a positive reverse transcriptase–polymerase chain reaction nasopharyngeal swab and/or serum antibody to SARS-CoV-2, who were attending a follow-up appointment at Chelsea and Westminster Hospital, a teaching hospital in London, England, were enrolled sequentially in the PHENOTYPE study. Written consent was obtained from all participants. Participants who were discharged from the hospital between March and June 2020 and assessed between June and September 2020 were eligible for inclusion.

Data Collection and Validation Tools

Acute hospital admission data were accessed using institutional electronic health records. During clinic visits, demographic and anthropometric data, clinical history, and blood test results were gathered, including complete blood count, renal profile, liver profile, bone profile, C-reactive protein level, D-dimer level, and fibrinogen level. Residual respiratory symptoms were assessed using validated tools: the modified Medical Research Council (mMRC) score (26) and the Leicester cough questionnaire (27).

CT Protocol

Participants were scanned with one of two 128-section multidetector row CT machines (Siemens Edge or Edge plus; Siemens Healthcare). Unenhanced thoracic high-resolution CT or, in participants with elevated D-dimer level, CT pulmonary angiography was performed with the following parameters: 1.0–1.5-mm-thick sections, 100 kVp or 120 kVp, reference milliampere second of 66 mAs or 105 mAs (for high-resolution CT and CT pulmonary angiography, respectively), median volume CT dose index of 4.2 mGy (IQR, 3.1–5.6 mGy), and median dose-length product of 149 mGy · cm (IQR, 106–210 mGy · cm). Iohexol (350 mg of iodine per milliliter) was the contrast material used. At the time of the first follow-up visit, the hospital restricted lung function testing to urgent cases (eg, as part of cancer diagnostics) because it was considered an aerosol-generating procedure. As such, in our study, formal lung function testing was limited to participants with abnormalities on chest CT scans and/or persistent breathlessness.

Participants with an abnormal CT scan at 3 months were invited for a repeat scan at 1 year after discharge coupled with assessment of self-reported breathlessness and lung function testing.

CT scans obtained during the participants' inpatient stay were not used for analysis in this study.

Image Analysis: Quantification of CT Abnormalities

All CT scans were reviewed by two thoracic radiologist observers (A.D. and S.R.D., both with >20 years of experience) blinded to all clinical and functional data. In consensus, observers quantified the overall extent of opacified lung and, for the abnormally opacified lung, the proportional extents of the following radiologic patterns: *(a)* ground-glass opacification, *(b)* consolidation, *(c)* linear or curvilinear band opacities, and *(d)* reticulation, all to the nearest 5%. The presence or absence of volume loss in individual lobes was recorded (0 = volume loss not present, 1 = volume loss present). Finally, the presence and/or severity of traction bronchiectasis and/or bronchiolectasis was graded semiquantitatively (0 = none, 1 = mild, 2 = moderate, and 3 = severe) and, when present, the number of lobes affected was recorded (up to a maximum score of 6). The lingula was scored as a separate lobe.

CT scans obtained at 1 year were compared side-by-side with the 3-month follow-up scan. For the 1-year CT scans, observers recorded whether there had been improvement, deterioration, or stability compared with the 3-month CT scan. Persistent abnormalities on the 1-year scan were quantified in the same manner as for the 3-month scan (see above).

Statistical Analysis

Continuous variables are expressed as medians and IQRs or means ± SDs. Categorical variables are reported as numbers and percentages. Comparisons between groups were performed using the two-sample Student *t* test or Mann-Whitney *U* test, as appropriate. Paired testing using Wilcoxon signed rank test was used to compare changes in CT scores. Categorical data were compared with the χ^2 test. Missing data within the Leicester cough questionnaire were accounted for by amending the scoring formula. The Spearman rank correlation method was used. $P < .05$ was considered to indicate a statistically significant difference. All statistical analyses were performed by an author

(B.V.) using software (Graphpad Prism version 9.0 [86] for Mac, GraphPad Software [*www.graphpad.com*]). Bonferroni correction was used as appropriate.

Results

Demographic Data at Hospital Admission

Eighty participants (mean age ± SD, 59 years ± 13; 53 men) were assessed. Table 1 shows the baseline demographic, inpatient, and follow-up characteristics. Figure 1 highlights the enrollment process. The initial follow-up visit was conducted at a median of 97 days (IQR, 86–121 days) after discharge. Common comorbidities included hypertension (23 participants, 29%), type II diabetes mellitus (18 participants, 23%), and asthma (11 participants, 14%). Most participants had no previous respiratory (65 participants, 81%) or cardiovascular (56 participants, 70%) comorbidity, and 42 participants (53%) were lifelong nonsmokers. The median hospital stay was 8 days (IQR, 3–15 days), with 32 participants (40%) requiring level 2 or 3 ventilatory support in the form of mechanical ventilation or noninvasive positive pressure ventilation, which includes continuous positive airway pressure or bi-level positive airway pressure ventilation.

Acute pulmonary embolism, necessitating therapeutic anticoagulation, was recorded in seven participants (8.8%) during the acute admission. All participants with pulmonary embolism needed mechanical ventilation (n = 4) or positive pressure ventilation (n = 3).

Respiratory Symptoms

Persistent cough (17 of 80 participants, 21%) and breathlessness (37 of 80 participants, 46%) were the most common respiratory symptoms at the 3-month follow-up, with a deterioration in the mMRC score in most participants reporting breathlessness (29 of 37 participants, 78%) (Table E1 [online]).

Blood Abnormalities

Blood results at admission and 3-month follow-up can be found in Tables E2 and E3 (online). Although most blood abnormalities had resolved at follow-up, a raised C-reactive protein level (13 of 80 participants, 16%), raised fibrinogen level (seven of 76 par-

Table 1: Demographic Data at Admission and Follow-up Characteristics in COVID-19 Survivors

Characteristic	Value at 3-month Follow-up (n = 80)	Value at 1-year Follow-up (n = 32)
Age (y)*	59 ± 13	62 ± 11
No. of men	53 (66)	21 (66)
Ethnicity		
White	39 (49)	13 (41)
Asian or Asian British	27 (34)	11 (34)
Black, African, Caribbean, or Black British	13 (16)	8 (25)
Other ethnic group	1 (1.3)	0 (0)
Comorbidities: respiratory		
Asthma	11 (14)	6 (19)
COPD	6 (8)	2 (6)
Obstructive sleep apnea	2 (3)	0
None	65 (81)	24 (75)
Comorbidities: cardiovascular		
Hypertension	23 (29)	11 (34)
IHD	6 (8)	3 (9)
Hypercholesterolemia	8 (10)	4 (13)
Atrial fibrillation	3 (4)	0
None	56 (70)	14 (44)
Other comorbidities		
T2DM	18 (23)	8 (25)
Previous VTE	4 (5)	1 (3)
Anxiety and/or depression	9 (11)	4 (13)
Smoking status at admission		
Current smoker	3 (4)	1 (3)
Ex-smoker	35 (44)	18 (56)
Nonsmoker	42 (53)	13 (41)
Length of hospital stay (d)†	8 (3–15)	8 (3–21)
Highest level of ventilatory support during inpatient stay		
Intubation	17 (21)	9 (28)
Positive pressure ventilation	15 (19)	5 (16)
Oxygen therapy only	43 (54)	18 (56)
No respiratory support	5 (6)	0
Time between discharge and follow-up visit (d)†	97 (86–121)‡	362 (361–370)
BMI at follow-up (kg/m^2)†	29 (26–33)§	28 (26–32)
Symptoms at follow-up visit		
Cough	17 (21)	4 (13)
Breathlessness	37 (46)	6 (19)

Note.—Except where indicated, data are numbers of participants, with percentages in parentheses. Self-reported ethnic groups wre defined in accordance with the 2021 Census of England and Wales (*https://www.ethnicity-facts-figures.service.gov.uk/style-guide/ethnic-groups*). BMI = body mass index, COPD = chronic obstructive pulmonary disease, IHD = ischemic heart disease, T2DM = type 2 diabetes mellitus, VTE = venous thromboembolism.

* Data are means ± SDs.

† Data are medians, with IQR in parentheses.

‡ Data are for 79 participants.

§ Data are for 72 participants.

ticipants, 9.2%), abnormal ferritin level (11 of 79 participants, 14%), and raised D-dimer level (14 of 79 participants, 18%) were commonly seen.

CT Abnormalities at 3-month Follow-up

Seventy-three participants underwent a 3-month CT examination at a median of 105 days (IQR, 95–141 days) following hospital discharge. Abnormalities on 3-month CT scans were present in 41 of the 73 participants (56%) (Figs 2, 3), with a median extent of 25% (IQR, 10%–60%; 95% CI: 15, 45). Ground-glass opacification (seen in 35 of 41 participants [47.9%]; median proportional extent, 16% [IQR, 3.5%–42%; 95% CI: 5, 35]) and linear or curvilinear bands (27 of 41 participants [36.9%]; median proportional extent, 3.8% [IQR, 0, 12; 95% CI: 0, 8]) were the dominant abnormalities on the 3-month CT scans. Reticulation (10 of 41 participants [14%]; median proportional extent, 0% [IQR, 0%–0.5%; 95% CI: 0, 0]) and consolidation (five of 41 participants [6.8%]; median proportional extent, 0% [IQR, 0%–0%; 95% CI: 0, 0]) were infrequently present. Nine of 41 participants (12%) had overt CT signs considered indicative of fibrosis at follow-up, namely traction bronchiectasis or bronchiolectasis (five participants, 6.8%) and/or volume loss (six participants, 8.2%).

The median age of the nine participants with CT features of fibrosis was 59 years (IQR, 56–67 years). The median length of hospital stay for these participants was 22 days

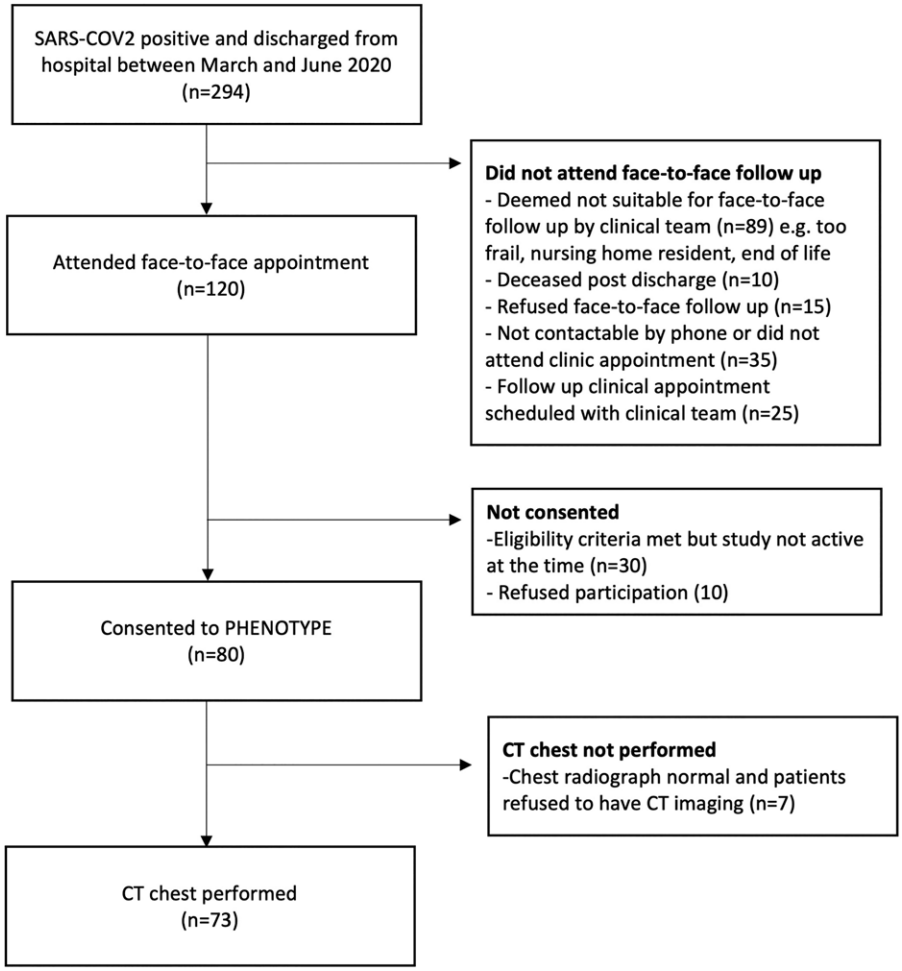

Figure 1: Study flowchart shows enrollment and recruitment.

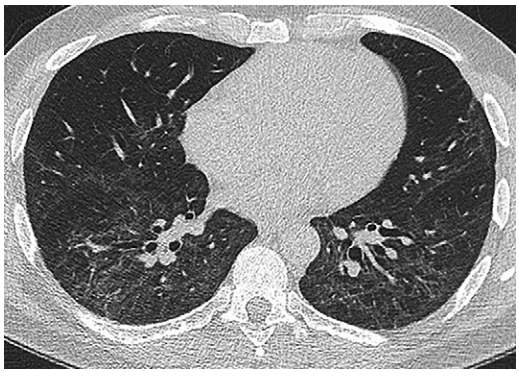

Figure 2: Axial unenhanced CT scan in a 48-year-old man 3 months after hospital discharge for COVID-19. Image shows predominant ground-glass opacities and a few delicate band opacities, principally in the lower lobes. There was no traction bronchiectasis or reticulation on any image section. (Note that the short segment of airway captured in longitudinal section in the right lower lobe was nondilated on sequential volumetric images sections.)

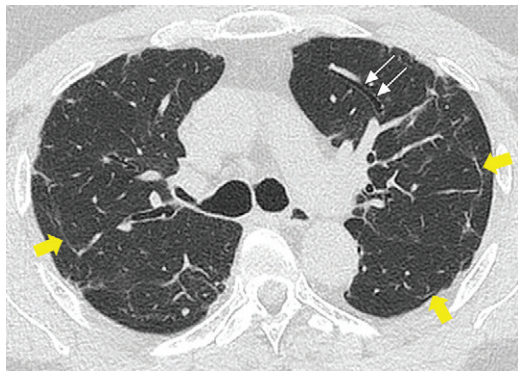

Figure 3: Axial unenhanced CT scan at the level of the carina in a 56-year-old man 3 months after discharge for COVID-19. Image shows multiple linear and curvilinear bands (yellow arrows) and more limited, subtle ground-glass opacification. There was no evidence of traction bronchiectasis. Note the normally tapering airway (white arrows) in the anterior segment of the left upper lobe.

(IQR, 5–50 days); eight of the nine participants (89%) were men, and participants had the following comorbidities: type II diabetes mellitus (six of nine participants, 67%), hypertension (five of nine participants, 55%), ischemic heart disease and hypercholesterolemia (two of nine participants for each, 22%), and asthma (one of nine participants, 11%). In addition, three of nine participants (33%) required positive pressure ventilation, five (55%) required mechanical

Table 2: Demographic Characteristics of Participants with Fibrosis at 3-month Follow-up Chest CT

Participant No.	Percentage Overall Parenchymal Abnormality at CT	Volume Loss	Gestalt Traction Severity*	Age (y)	Sex	Ethnicity	Comorbidities	LOS (d)	Maximum Respiratory Support
1	60	Yes	1 (2)	73	M	Asian or Asian British	IHD, HTN, T2DM	12	Positive pressure ventilation (CPAP)
2	5	Yes	NA	68	M	White	IHD, HTN, T2DM	6	Oxygen
3	25	No	2 (1)	56	M	Black, Black British, Caribbean, or African	DVT in 2018	5	Positive pressure ventilation (CPAP)
4	70	Yes	NA	55	M	Asian or Asian British	Asthma, HTN, T2DM	32	Mechanical ventilation
5	75	Yes	NA	65	M	Black, Black British, Caribbean, or African	HTN, T2DM	8	Positive pressure ventilation (CPAP)
6	70	No	1 (2)	52	M	White	None	50	Mechanical ventilation
7	80	No	2 (3)	66	F	Black, Black British, Caribbean, or African	T2DM, high cholesterol	22	Mechanical ventilation
8	30	Yes	1 (4)	59	M	Black	None	37	Mechanical ventilation
9	40	Yes	NA	58	M	Asian	HTN, T2DM	49	Mechanical ventilation

Note.—Self-reported ethnic groups were defined in accordance with the 2021 Census of England and Wales (*https://www.ethnicity-facts-figures.service.gov.uk/style-guide/ethnic-groups*). CPAP = continuous positive airway pressure, DVT = deep vein thrombosis, HTN = hypertension, IHD = ischemic heart disease, LOS = length of stay, NA = not applicable, T2DM = type 2 diabetes mellitus.

* Numbers in parentheses are numbers of lobes.

Table 3: Intergroup Comparisons of Participants according to Level of Respiratory Support and Presence or Absence of Abnormalities, GGO, or Bands on 3-month Follow-up Chest CT Scans

CT Features	Mechanical Ventilation		*P* Value	Odds Ratio	Adjusted *P* Value	Mechanical or Positive Pressure Ventilation		*P* Value	Odds Ratio	Adjusted *P* Value
	Yes	No				Yes	No			
CT finding										
Normal	2	30	.004	7.8 (1.7, 36)	.024	7	25	.006	4.1 (1.5, 11)	.036
Abnormal	14	27				22	19			
GGO										
Present	13	22	.003	6.9 (1.8, 24)	.018	20	15	.004	4.3 (1.6, 12)	.024
Absent	3	35				9	29			
Bands										
Present	10	17	.015	4 (1.2, 14)	.09	17	10	.002	4.8 (1.7, 14)	.012
Absent	6	41				12	34			

Note.—Statistical analysis was performed with the χ^2 test. Raw *P* values and adjusted *P* values (Bonferroni-Dunn correction) for multiple analyses are displayed. Numbers in parentheses are the 95% CIs. GGO = ground-glass opacification.

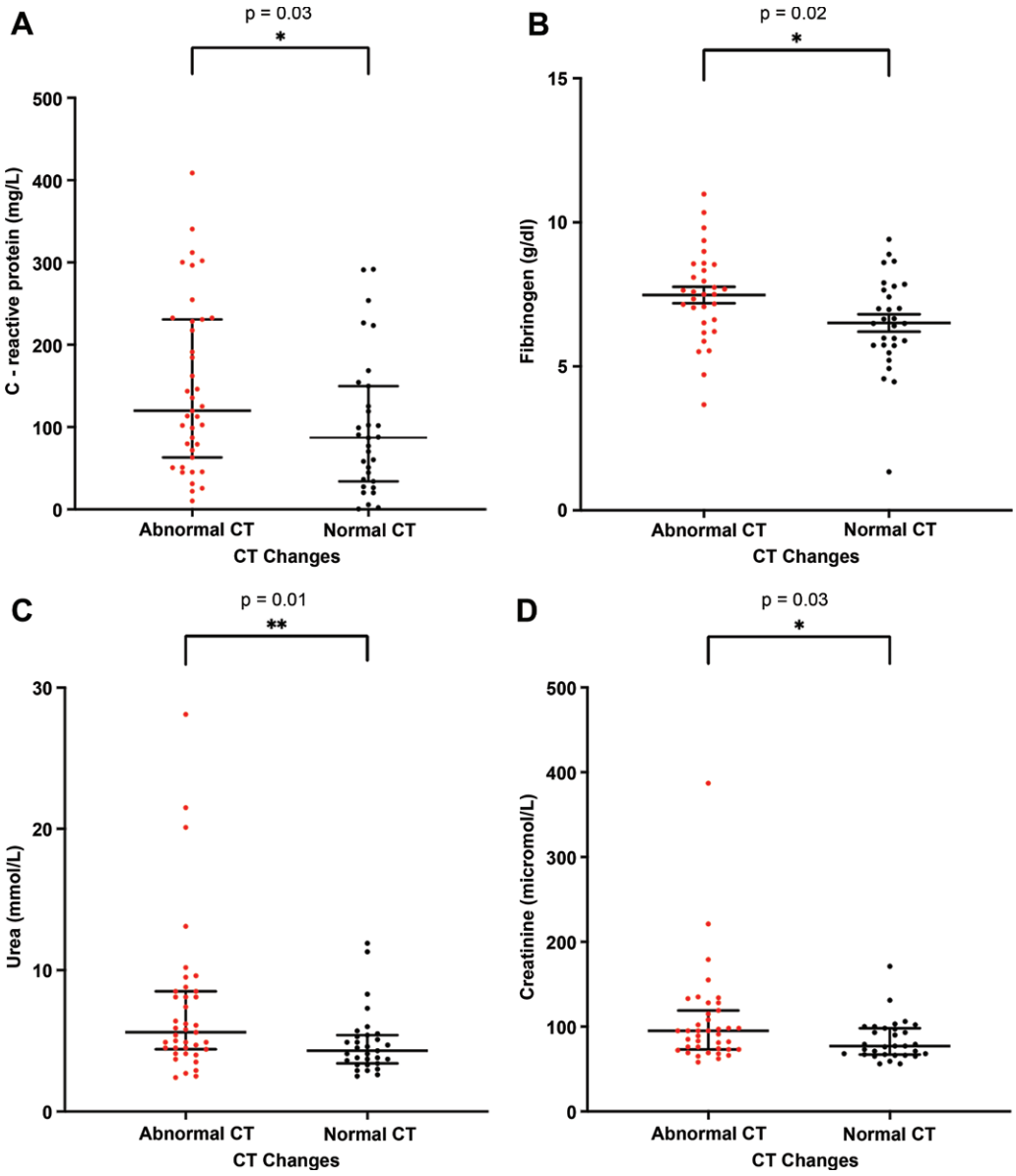

Figure 4: Scatterplots show relationship between admission blood parameters **(A)** C-reactive protein level, **(B)** fibrinogen level, **(C)** urea level, and **(D)** creatinine level in participants with and without CT changes at 3-month follow-up. Comparisons were made using the two-sample Student *t* test and Mann-Whitney *U* test. Medians and IQRs are shown. * = $P \leq .05$, ** = $P \leq .01$.

ventilation, and one (11%) required oxygen therapy alone (Table 2).

On the basis of the overall CT extent of abnormal lung, participants were divided into three severity groups, as follows: mild (<30% abnormal lung), moderate (30% to <60%), and extensive (≥60%). In the 41 participants with persistent CT abnormalities at follow-up, 21 (51%) were in the mild group, seven (17%) in the moderate group, and 13 (32%) in the extensive group.

Relationship between Abnormalities at 3-month CT and Respiratory Symptoms

We found no evidence of a difference in participant-reported breathlessness between those with and without CT abnormalities (21 of 41 participants with an abnormal CT scan vs 15 of 32 with a normal CT scan; $P = .71$) or when comparing among the mild, moderate, and extensive CT severity groups (10 of 21 participants with mild severity, three of seven with moderate severity, and eight of 13 with extensive severity; $P = .66$). Similarly, a change in mMRC was not linked to the presence or absence of CT abnormalities (16 of 41 participants with an abnormal CT scan vs 13 of 32 with a normal CT scan; $P = .89$) or their extent (seven of 21 participants with mild severity, two of seven with moderate severity, and six of 13 with severe; $P = .41$).

Relationship between Abnormalities at 3-month CT, Respiratory Support, and Blood Profile at Admission

The relationships between CT abnormalities and *(a)* levels of respiratory support required and *(b)* blood parameters at admission are shown in Table 3 and Figures 4 and E1 (online), respectively. Abnormalities on 3-month CT scans were related

Table 4: Demographic Characteristics, Acute Admission Data, and Admission Blood Results of Participants with Abnormal versus Normal CT Scans at 3-month Follow-up

Characteristic	Normal Range	Abnormal CT Scans (n = 41)	Normal CT Scans (n = 32)	Odds Ratio	*P* Value	95% CI
Age (y)*	≥18	62 ± 10	57 ± 12		.004	
Male sex†		28 (68)	20 (63)	1.3	.61	0.5, 3.5
BMI (kg/m^2)		28.7 (25–31)	29.3 (26.89–34.9)		.14	
Nonwhite†		23 (56)	16 (50)	1.3	.60	0.5, 3.2
Smoker or ex-smoker†		23 (56)	12 (38)	2.1	.11	0.9, 5.7
OAD†		8 (20)	8 (25)	0.7	.57	0.3, 2.1
Cardiac history†		14 (34)	7 (22)	1.8	.25	0.6, 4.9
T2DM†		11 (27)	6 (19)	1.6	.42	0.5, 5.2
Mechanical ventilation†		14 (34)	2 (6.3)	7.8	.004	1.7, 36
Positive pressure ventilation†		22 (54)	7 (22)	4.1	.006	1.5, 11
Breathlessness†		21 (51)	15 (47)	1.2	.71	0.5, 2.9
LOS (d)		10 (5.3–27)	6.0 (3.0–8.8)		.008	
White blood cell count (×10^9/L)	4.2–10.6	7.2 (5.9–8.9)	7.1 (5.5–8.4)		.35	
Hemoglobin level (g/L)*	130–160	140 ± 14	143 ± 11		.37	
Platelet count (×10^9/L)	130–370	242 (176–317)	230 (174–267)		.37	
Neutrophil level (×10^9/L)	2.1–7.1	6.1 (4.2–7.6)	5.6 (3.7–7.1)		.27	
Lymphocyte level (×10^9/L)	1.1–3.6	0.9 (0.7–1.5)	1.0 (0.73–1.1)		.74	
D-dimer level (μg/L)	<500	1364 (853–2685)	1143 (494–1571)		.25	
Fibrinogen level (g/L)*	1.9–4.3	7.5 ± 1.6	6.512 ± 1.6		.02	
Ferritin level (μg/L)	20–300	742 (540–1961)	468 (329–1498)		.18	
Sodium level (mmol/L)*	133–146	136 ± 3.5	136 ± 4.5		.57	
Potassium level (mmol/L)	3.5–5.3	4.3 (4.0–4.7)	4.1 (3.7–4.4)		.11	
Urea level (mmol/L)	2.5–7.8	5.6 (4.4–8.5)	4.3 (3.4–5.4)		.001	
Creatinine level (μmol/L)	60–125	95 (73–119)	77 (67–98)		.03	
eGFR (mL/min/1.73 m^2)	>90	71 (50–90)	84 (69–90)		.06	
ALT level (U/L)	0–45	37 (23–52)	29 (22–65)		.48	
Albumin level (g/L)	35–50	32 (31–36)	34 (31–39)		.09	
CRP level (mg/L)	0–5	120 (63–21)	87 (34–150)		.03	

Note.—Except where indicated, data are medians, with IQR in parentheses. Statistical analyses were performed using the Mann-Whitney *U* or two-sample Student *t* test or the χ^2 test, with odds ratios and 95% CIs. Nonwhite refers to Asian or Asian British, Black, Black British, Caribbean or African, mixed or multiple ethnic groups or other ethnic group, defined according to the list of ethnic groups provided by the 2021 Census of England and Wales (*https://www.ethnicity-facts-figures.service.gov.uk/style-guide/ethnic-groups*). ALT = alanine aminotransferase, BMI = body mass index, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, LOS = length of stay, OAD = obstructive airways disease, T2DM = type 2 diabetes mellitus.

* Except where indicated, data are means ± SDs.

† Except where indicated, data are numbers of participants, with percentages in parentheses.

to length of hospital stay (mean, 17 days ± 17 vs 7.4 days ± 7.1; *P* = .008), age (mean, 62 years ± 10 vs 57 years ± 12; *P* = .04), and admission blood markers (C-reactive protein, fibrinogen, urea, and creatinine levels). The proportion of participants with an abnormal CT scan at follow-up was higher in participants requiring mechanical ventilation (odds ratio: 7.8; 95% CI: 1.7, 36.1; *P* = .004) and in those requiring mechanical ventilation or positive pressure ventilation (odds ratio: 4.1; 95% CI: 1.5, 10.7; *P* = .006). Table 4 shows the demographic characteristics, admission data, and blood abnormalities in greater detail.

We found no evidence of differences in the time interval (days) between discharge and CT in those with CT abnormalities versus those without (mean, 117 days ± 34 for participants with abnormal CT scans vs 135 days ± 49 for those with normal CT scans; *P* = .22) and no correlation between percentage parenchymal involvement and time after admission (*r* = 0.02, *P* = .84) or time after discharge (*r* = −0.16, *P* = .18).

Pulmonary Function Tests and Relationship with Abnormalities on 3-month CT Scans

Pulmonary function testing was performed in 39 of 73 participants undergoing CT imaging (52%), with one participant excluded due to poor technique. The median interval between CT and pulmonary function testing (all performed as outpatients) was 60 days (IQR, 37–87 days). CT scans were abnormal in 28 of the 38 participants (74%) undergoing pulmonary function testing. Table E4 (online) shows a summary of the lung function test results.

Reduced gas transfer (transfer factor of the lung for carbon monoxide [TLCO]) was the most common lung function abnormality in participants with an abnormal CT scan (10 of 28

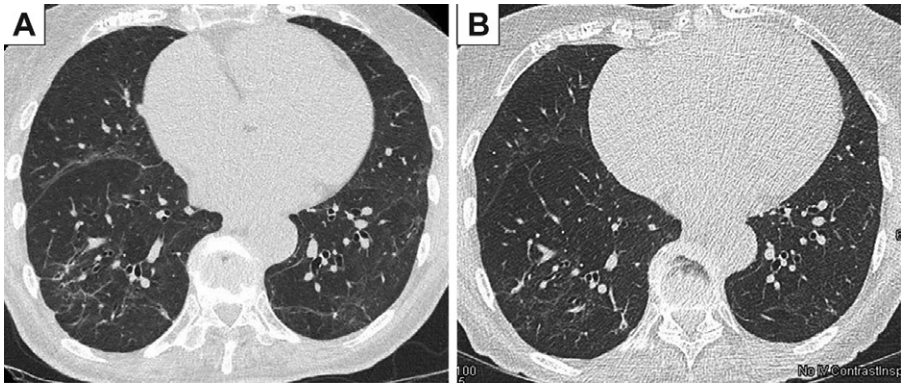

Figure 5: Paired axial unenhanced CT scans in an 83-year-old woman at **(A)** 3 months and **(B)** 1 year after hospital discharge for COVID-19. Images show significant (albeit incomplete) and progressive resolution of ground-glass opacification and band opacities in the lower lobes at 1-year follow-up.

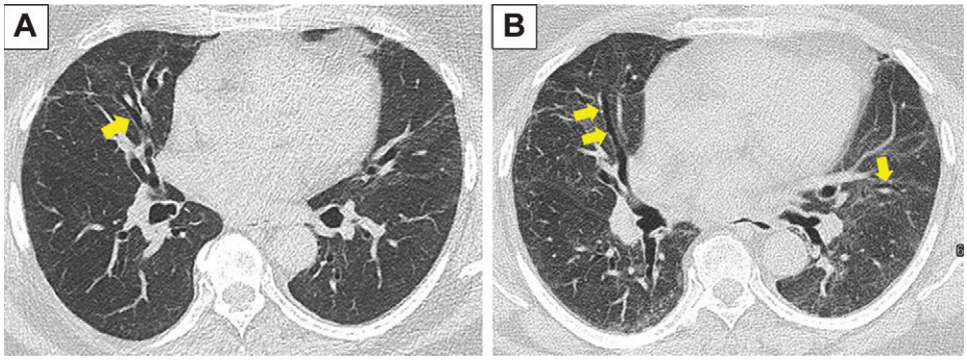

Figure 6: Paired axial unenhanced CT scans in a 59-year-old man at **(A)** 3 months and **(B)** 1 year after hospital discharge for COVID-19. Images show widespread residual bilateral ground-glass opacification, a few band opacities, and, importantly, evidence of traction bronchiectasis in the middle and left lower lobes (arrow in **A**) at 3 months. There is a reduction in the extent of ground-glass opacification and bands but with persistent traction brochiectasis (arrows in **B**) at 1-year follow-up.

participants, 36%). In participants with extensive CT abnormalities (ie, ≥60% abnormality), disease extent at CT showed negative correlation with percent predicted forced expiratory volume in 1 second ($r = -0.74$, $P = .01$), forced vital capacity ($r = -0.80$, $P = .004$), and total lung capacity ($r = -0.78$, $P = .006$) and positive correlation with carbon monoxide transfer coefficient ($r = 0.62$, $P = .05$). There was no correlation between CT extent and percent predicted T_{LCO} ($r = 0.27$, $P = .41$) (Fig E2 [online]). Figure E3 (online) shows the relationship between the number of lobes affected in those with features of traction bronchiectasis at CT ($n = 5$) and percent predicted T_{LCO} ($r = -0.95$, $P = .17$).

CT Abnormalities at 1-year Follow-up and Relationship with Symptoms and/or Functional Indexes

Of 41 participants with an abnormal finding on 3-month CT chest scans, 33 (80%) underwent repeat CT imaging between March 2 and May 7, 2021, at a median of 364 days (range, 360–366 days) after discharge. Tables 1 and E5 (online) and Figure E4 (online) show the cohort undergoing repeat imaging; CT scans from one participant treated with corticosteroid after discharge were excluded. Follow-up CT scans at 1 year were normal in five of the 32 participants (16%) and stable in six (19%), with no change in the overall extent of abnormalities (median residual overall extent, 7.5%; IQR, 5%–17.5%; 95% CI: 5, 25), ground-glass opacification (median residual overall extent, 5%; IQR, 0–10.8; 95% CI: 0, 25), and bands (median residual overall extent, 2.5%; IQR, 0%–6%; 95% CI: 0, 9). In 21 of the 32 participants (66%) there was improvement with a median reduction in extent of 17.5% (IQR, 10%–40%; 95% CI: 10, 35) in overall extent, 11.5% (IQR, 1.9%–39.8%; 95% CI: 4, 35) in ground-glass opacification, and 0.5% (IQR, 0%–2.5%; 95% CI: 0, 2) in bands. Figures 5 and 6 show serial CT changes in two participants.

Persistent breathlessness was reported by six of the 32 participants (19%) at 1 year, with five (16%) reporting breathlessness at the time of the 3-month chest CT examination, which resolved at 1 year, despite no radiologic improvement. There were no reports of breathlessness in participants with a normal CT scan at 1 year. Lung function testing was feasible in 26 of the 32 participants (81%) at a median of 365 days (IQR, 362–376 days) after discharge (Table E6 [online]). There was no correlation between the residual overall CT extent at 1 year and lung function parameters (Fig E5 [online]).

We found evidence of statistically significant improvements in the overall CT extent of abnormality and the extent of ground-glass opacification but not bands at 1-year follow-up when compared with the CT scan at 3 months. As compared

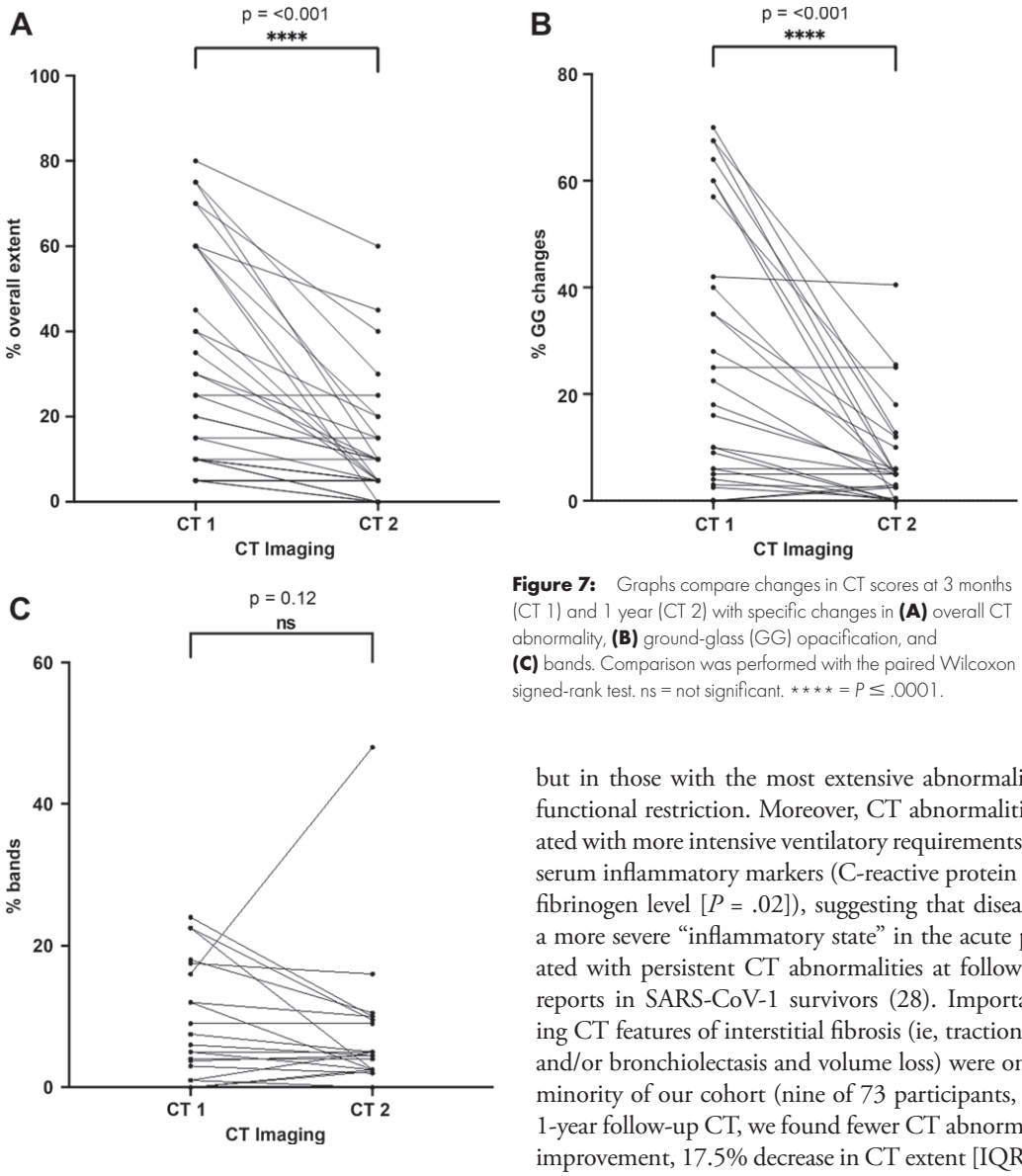

Figure 7: Graphs compare changes in CT scores at 3 months (CT 1) and 1 year (CT 2) with specific changes in **(A)** overall CT abnormality, **(B)** ground-glass (GG) opacification, and **(C)** bands. Comparison was performed with the paired Wilcoxon signed-rank test. ns = not significant. **** = $P \leq .0001$.

with band opacities, the reduction in extent of ground-glass opacification was more striking and there was a positive correlation between improvement in overall CT scores and both the ground-glass component ($r = 0.88$, $P < .001$) and bands ($r = 0.74$, $P = .001$) (Figs 7, E6 [online]). There was no evidence of progressive disease at sequential imaging.

Discussion

Our prospective study of COVID-19 survivors discharged from the hospital was performed to better understand the clinical, physiologic, and radiologic recovery with time. Our study has shown that, in addition to symptoms, persistent physiologic and radiologic abnormalities are common at 3-month follow-up. Radiologic abnormalities were present in 41 of 73 participants (56%) at 3-month follow-up, with the most common findings being ground-glass opacification (35 of 73 participants, 48%) and bands (27 of 43 participants, 37%). Morphologic abnormalities on CT scans were not linked to dyspnea ($P = .71$) or a change in modified Medical Research Council score ($P = .89$), but in those with the most extensive abnormalities, there was functional restriction. Moreover, CT abnormalities were associated with more intensive ventilatory requirements ($P = .004$) and serum inflammatory markers (C-reactive protein level [$P = .03$], fibrinogen level [$P = .02$]), suggesting that disease severity and a more severe "inflammatory state" in the acute phase is associated with persistent CT abnormalities at follow-up, mirroring reports in SARS-CoV-1 survivors (28). Importantly, convincing CT features of interstitial fibrosis (ie, traction bronchiectasis and/or bronchiolectasis and volume loss) were only present in a minority of our cohort (nine of 73 participants, 12%) (21). At 1-year follow-up CT, we found fewer CT abnormalities (median improvement, 17.5% decrease in CT extent [IQR, 10%–40%]). None of the study participants showed progression of CT findings at 1-year follow-up.

Our findings are in line with recent reports (3,17) where persistent clinical, functional, and radiologic abnormalities were seen up to 3 months after hospital discharge. The improvement in radiologic features with time accords with data from SARS-CoV-1, in which the prevalence of parenchymal abnormalities also decreased with time (6,29–30). Our findings align with those in the most recent study by Wu et al (31), who prospectively followed-up 83 nonventilated patients for up to 1 year and found progressive improvement in the majority but a few with residual functional impairment and persistent radiologic abnormalities. The improvement in both ground-glass opacification and bands in our study is an important finding that challenges the assumption that bands reflect established fibrosis. In addition, our finding of fibrosis in only nine of the 73 participants (12%) at 3-month follow-up is important to stress given the recent tendency in the literature to readily ascribe a label of "post-COVID interstitial lung disease" or "COVID-related fibrosis" on the basis of CT findings alone (21).

Lung fibrosis is known to complicate diffuse alveolar damage or acute respiratory distress syndrome. Indeed, a fibroproliferation phase of variable severity is part of the natural history of diffuse alveolar damage (14,32,33). Furthermore, fibrosis in patients with acute respiratory distress syndrome may be iatrogenic, caused by barotrauma (34); therefore, some of the features seen at CT after COVID-19 may be a consequence of mechanical ventilation or associated lung injury, rather than due to COVID-19. Recent data suggest that the prevalence of fibrosis after COVID-19 ranges from 39% to 67% (18,21,35,36). However, the reliance almost wholly on CT features (without histopathologic corroboration) and vague terminology is problematic. Nonspecific radiology terms (eg, fibrotic bands or stripes) and the amalgamation of different radiologic signs—including parenchymal bands, traction bronchiectasis, and honeycombing—under a generic "fibrotic group" warrants scrutiny. Finally, interobserver variability for interpreting nonspecific signs such as "irregular interfaces" adds a further challenge, which is seldom highlighted in earlier studies (37).

In our study, the dominant CT patterns at follow-up were ground-glass opacification and linear or curvilinear bands. Ground-glass opacification at CT indicates a region of lung from which air has been partially displaced (38). Accordingly, ground-glass opacification may be a manifestation of an interstitial lung disease, airspace abnormality, or some combination of the two (39). In COVID-19 survivors, we postulate that ground-glass opacities (in the absence of traction bronchiectasis) represent resolving diffuse alveolar damage or acute respiratory distress syndrome, in which there is substantial histopathologic heterogeneity (40). Therefore, making a diagnosis of established lung fibrosis on the basis of ground-glass opacification alone may overestimate the prevalence of fibrosis (33). The view that all bands denote fibrosis is also presumptuous: other pathologic processes, for instance subsegmental atelectasis (34) and organizing pneumonia (41) (incidentally, a frequent pathologic finding in COVID-related acute respiratory distress syndrome) (37), may manifest in this way on CT scans. One of the strengths of our study is that in contrast with earlier studies, we have restricted our CT evaluation to accepted radiologic terms (39). We have also captured the spectrum of disease severities requiring hospital admission, rather than restricting our cohort to participants requiring level 2 or 3 ventilatory support—a subgroup more likely to have significant sequelae and over-represented in the current literature (18,21).

Our study has limitations. First, the absence of histopathologic confirmation is a limitation of our study, making inferences based on surrogate CT signs mandatory. Second, our study includes a relatively small numbers of study participants. Therefore, it is also possible that some relationships between variables were not identified due to underpowering, particularly in relation to subgroup analyses (18,21). Third, we had a limited proportion of participants with full lung function results. Fourth, breathlessness was assessed using participant-reported symptoms and the mMRC score. The latter score has a limited range of options and can be difficult to interpret. Furthermore, calculating premorbid mMRC is prone to recall bias. Especially in this cohort, difficulty differentiating between breathlessness and fatigue, weight gain between visits, and deconditioning call into question the validity and cause of patient-reported breathlessness, which may explain the lack of association between patient-reported breathlessness and persistent radiologic findings. Finally, multiple hypotheses testing means that $P < .05$ might not necessarily be statistically significant.

In summary, this study has shown that patient symptoms, abnormalities on CT scans, and changes in lung function are relatively common after COVID-19 and may persist well up to 12 months after discharge. In 81% of study participants (26 of 32), radiologic abnormalities regressed further between the 3-month and 12-month CT scan. Data from larger cohorts undergoing longer follow-up are likely to further clarify these results.

Author contributions: Guarantors of integrity of entire study, **B.V., S.R.D., P.L.S.**; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, **B.V., S.R.D.**; clinical studies, **B.V., J.T., A.D., S.R.D., P.L.S.**; statistical analysis, **B.V.**; and manuscript editing, all authors

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